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AUDIOMETRY DEVICE BASED ON COCHLEAR MICROPHONIC POTENTIALS

A DISSERTATION PRESENTED

BY

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ABSTRACT

The cochlear microphonic potentials are nano-sized potentials produced in the outer hair cells of the cochlea. This signal has very special properties that might lead to reach an objective audiometry system. However, the research process needed is hard and long. The “Instituto de investigación Sanitaria Gregorio Marañón” (IiSGM) decided to start a collaboration with the company Zero Entropy S.L in order to develop an objective audiometry device based on cochlear microphonic potentials. The first step is to understand what is going on in the hearing physiology and the cochlear microphonic potentials production. Secondly, the understanding of the socio-economic and legal feasibility of the project is needed. Finally, the implementation of a new CMP detecting system has to be tested and its results analyzed.

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“The most important thing in communication is hearing what isn’t said”

Peter F. Drucker

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MOTIVATION AND OBJECTIVES

1.1 Motivation

This project was born more than 20 years ago in the curious mind of a retired physician, Julio Sanjuan Juaristi, whose main aim was to develop an audiometry system that would not require an active collaboration of the subject of study. In other words, this audiometric method is intended to be completely objective in comparison to the present audiometry system. This new idea was presented at the beggining of June 2015 in the ‘Instituto de investigación Sanitaria of the Gregorio Marañón’ (IiSGM). The main motivation for this project was thus to validate this innovative idea by reimplementing the solution with modern technology and carry out a feasibility study, both from technical and business model standpoints. Another motivation was to try to contribute to the understanding of the exciting, complex and controverted auditive physiology; in particular, the mechanical cochlear function just before the nerve impulses’ action potentials are generated and sent to the brain.

1.2 Objectives

This bachelor thesis has several objectives:

- To review the hearing system physiology, in particular the inner ear, cochlear microphonic potentials and conventional audiometry as compared to this the new cochlear microphonic audiometry.
- To carry out an market pre-evaluation before a definitive market analysis is done.
- To implement a new proof of concept of the device, based on modern hardware and software tools, and to verify the technical feasibility of the solution.

1.3 Project structure

Each objective will be covered by one chapter of this document. The final two chapters will be devoted to conclusions and future work and references respectively.

“Hearing is one of the body’s five senses, however listening is an art”

Frank Tyger

2

INTRODUCTION AND STATE OF THE ART

2.1 PHYSIOLOGY OF AUDITION

Every living being on Earth has millons of disparate receptors which help communicating with the surrounding environment, thus adapting to it. Those receptors have a specific part devoted to fullfil their particular function and another part that links them to the central nervous system. The information that is conveyed from the receptors is used by the brain to keep the organism’s homeostasis; being the homeostasis the tendency towards equilibrium. In humans, there are five different senses which are hearing, sight, smell, taste and touch. In this chapter, the hearing system anatomy and physiology will be described.

The hearing system is an incredible and fast piece of engineering that is able to transduce sound vibrations of 0.2-0.4 nanometers of amplitude into electrical signals. Those signals are processed in the primary auditory cortex, located in the brain temporal lobe. The hearing system is divided into three separated regions, which are the outer, the middle and the inner ear. As humans, we have all this structures twice, one for each ear; This is really

useful due to the fact that allows humans to have stereophonic perception, contributing to identify were an emitter source is.

So as to understand hearing, it is neccesary to know the sound waves characteristics. Sound waves have two main parameters that define them: frequency and intensity. The frequency determines the sound pitch of a sound wave; the higher the frequency the higher the sound pitch. The audible range in humans is between 10-20 Hz and 20 kHz. The intensity is the amplitude of the sound wave and it is measured in decibels (dB). The hearing threshold is set as 0 dB at 1 kHz; when a sound wave intensity exceeds the 120 dB, the sound is painful for the subject.

The outer ear is formed by an elastic cartilage structure called the auricle, whose function is collecting the sound waves thanks to its characteristic convoluted structure, the external auditory canal that leads the sound pressure waves towards a thin membrane called eardrum (formally known as tympanic membrane). The eardrum is a thin membrane formed by epithelium and cartilage that is hit by the sound waves and transform them into vibrations. The eardrum moves back and forth transmitting the vibration to the ossicles in the inner ear. The speed of the tympanic membrame vibration depends on the sound frequency.

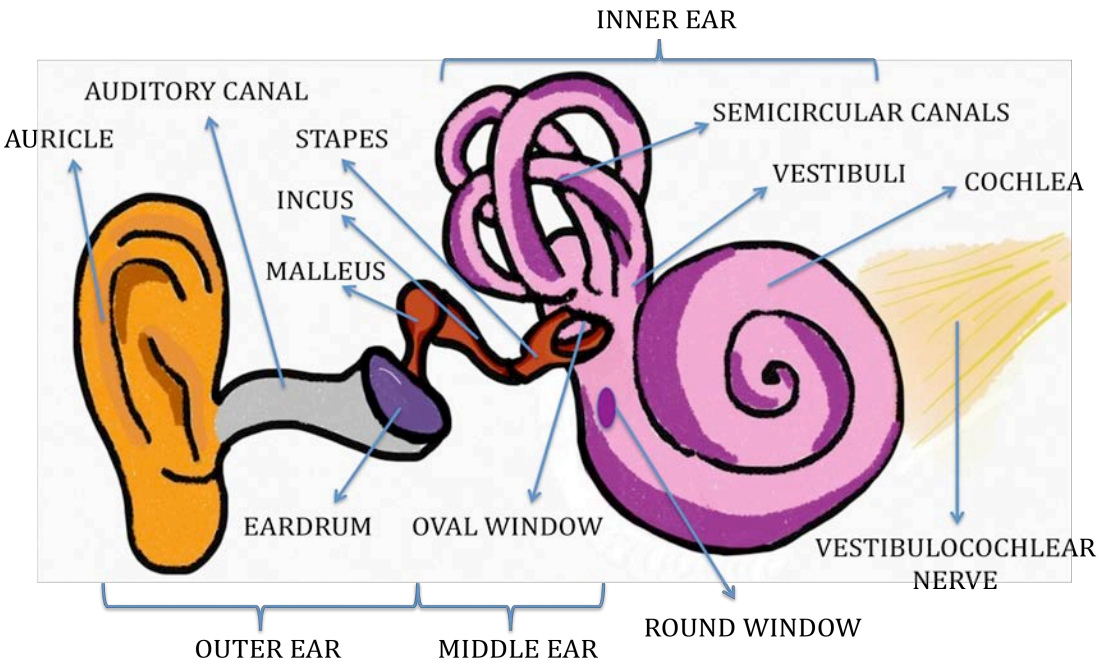

FIGURE 1: DIAGRAM HEARING SYSTEM

The middle ear is a tiny cavity at the other side of the eardrum that contains the three auditory ossicles, which are the malleus, incus and stapes (or hammer, anvil and stirrup respectively). The ossicles chain has the function of adjusting the impedance from the air to the fluid in the inner ear (the perilymph) and are held in place inside the middle ear thanks to synovial joints. The malleus is connected to the internal surface of the tympanic membrane and the stapes is connected to the oval window that is the entrace to the inner ear. Besides synovial joints there are two muscles connected to the ossicles that play an important role in the physiology of the vibrations transmission depending on the stimuli intensity; The first one is the tensor tympany muscle that is in charge of preventing damage to the inner ear, when there are loud noises this muscle increases tension in the eardrum, thus limiting its movement. The second muscle is the stapedius muscle which has the function of protecting the oval window (entrance to the inner ear) against load noises stimuli by dampening the stapes movement.

When a very sudden noise is emitted by a source both muscles have a small period to react, therefore transmiting the entire vibration impact through the ossicle chain and damaging the inner ear.

Inside the middle ear cavity there is a tube that connects the middle ear with the nasopharynx (throat superior part), the Eustachian tube; this tube has the function of equaling the pressure of the middle ear with the atmospheric pressure.(Tortora G. J., 2009)

2.2 Inner ear: cochlea

The inner ear or labyrith is a set of convoluted canals in charge of both the hearing and balance function. However, specific funcions of different structures inside the inner ear still have a difficult interpretation and need further research.

The inner ear is divided into a bony labyrinth and a membranous labyrinth. The former can also be segmented into three parts: three semicircular canals (this structures are in charge of the balance function; they contain a jelly-like fluid that moves inside the semicircular canals activating some receptors that send information to the brain in order to define the position of the subject in

space), vestibule (oval central protion of the bony labyrinth) and cochlea. The latter is an structure formed by several epithelial sacs and tubes inside the bony structure that in general keeps the same shape as the bony labyrinth. The epithelial membranous labyrinth is filled with endolymph.

The cochlea is a spiral bony structure, similar to a snail shell, in charge of the hearing function. It is divided into three cavities: scala vestibuli (ends at the oval window), scala media (contains the endolymph) and scala tympani (ends at the round window). The perilymph fluid that fills both the scala vestibuli and the scala tympani is continuous along those cavities. These cavities connect through an opening found at the apex of the cochlea called helicotrema. The basilar membrane separates the cochlear duct from the scala tympani and the vestibular membrane separates the cochlear duct from the scala vestibuli. The stapes of the middle ear transmits the vibration to the oval window membrane and immediately to the perilymph of the scala vestibuli and afterwards to the perilymph of the scala tympani. (Tortora G. J., 2009)

2.2.1 The cochlea in other species

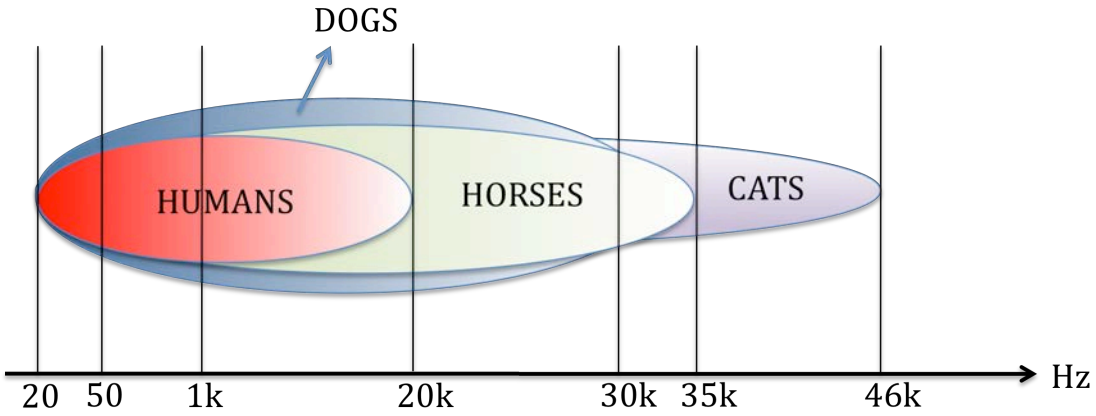

Figure 2: Scheme audible frequency range in several species

The cochlea size varies considerably depending on the particular species. The laboratory mouse (*Mus musculus*) cochlea has barely 3 milimeters of diameter, whereas an African elephant (*Loxodonta africanus*) cochlea, which was used in one experiment by the Nobel prize winner George von Békésy, has 15 centimeters. According to the amount of frequencies that the species are able to distinguish they have several sensorial receptors to do

so. Humans, for instance, need higher sensitivity in order to improve oral communication skills.

Depending on the function, the cholea structure has evolved so as to adapt to the medium where certain species dwell and to increase its efficiency. The diagram of figure 2, shows the range of frequencies that can be detected by cats (from 20 to 46,000 Hz), horses (from 20 to 35,000), dogs (from 20 to 30,000 Hz), and humans (20 to 20000 Hz). Regarding mice, rats and guinea pigs, animals oftenly used in the lab, the have an auditory frequency range of 400-40,000 Hz, 200-40,000 Hz, and 100-35,000 Hz respectively.

In other case such as in fishes, the cohlea has dissappeared; Throughout its middle ear they have a type of hair cells (shown in red in the figure 3) that allows them to feel vibrations.(Sanjuán Juaristi, The cochlea in several species, 2016)

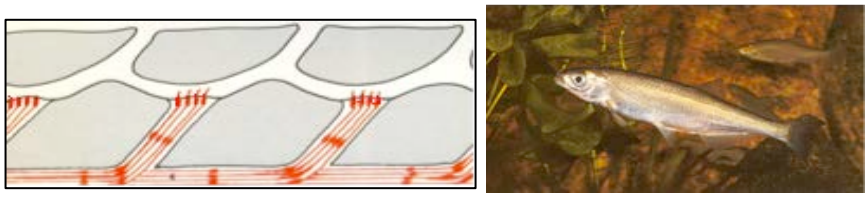

FIGURE 3: SCHEME FISH HEARING SYSTEM .(Sanjuán Juaristi, The cochlea in several species, 2016)

2.3 OUTER HAIR CELLS

The Organ of Corti is a coiled sheet that rests along the basilar membrane and it is formed by epithelial cells, supporting cells and about 16,000 hair cells. There exist two types of hair cells: inner and outer. The outer hair cells are arranged in three rows whereas the inner hair cells are arranged in one row. Hair cells are named this way due to the fact that they have hairlike microvilli, embedded in the gelatinous tectorial membrane. This microvilli are arranged according to graded height along the hair cells of the Organ of Corti.

The vibrations in the perilymph create pressure waves inside the endolymph of the cochlear duct, this causes the basilar membrane to vibrate and therefore moving the body of the hair cells against the microvilli embedded in the tectorial membrane. The hair cell stimulation produces changes in the

receptor potential that leads to the generation of nerve impulses. The basilar membrane has an structure distribution that vibrates and detects higher frequencies (20 kHz) in the portion closer to the oval window, and detects low frequencies (10 Hz) at the helicotrema where the basilar membrane is more flexible and wider.(Tortora G. J., 2009)

Focusing on the outer hair cell structure, the electrical arrangement can be modelled by a dipole of 25 micrometers length and with a biological difference in potential around 80 microvolts between the microvilli and the cell body. Along the basilar membrane the dipole lenght ranges between 25 to 70 micrometers according to Dr. Sanjuan's publications.(Sanjuán Juaristi, Conventional audiometry versus cochlear microphone audiometry, 2007)

The outer hair cells seem to react like very narrow bandwidth analogic active filters that react when the stimuli matches an specific frequency band.

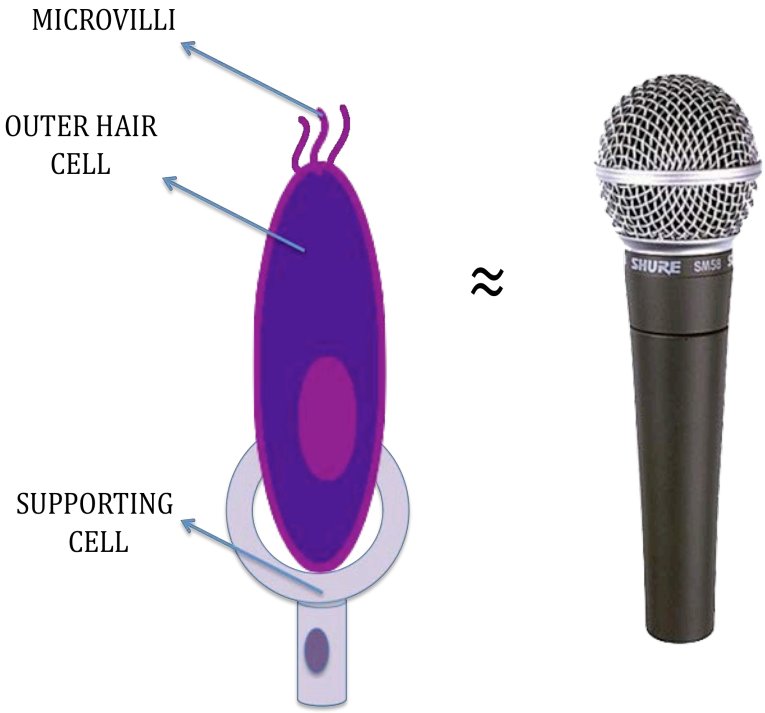

FIGURE 4: DIAGRAM OF AN OUTER HAIR CELL (LEFT) AND MICROPHONE (RIGHT)

2.4 COCHLEAR MICROPHONIC POTENTIALS

Since the eighties decade of the twentieth century, Dr. Julio Sanjuan Juaristi, who is a retired otorhinolaryngologist, has been researching on cochlear microphonic potentials (CMPs) with his group in the Ramon y Cajal

Hospital in Madrid. The theory and hypothesis below might be an alternative to the other theories related to this topic.

As far as it is known, when the basilar membrane vibrates the cilia of each outer hair cell are pressed against the tectorial membrane, causing the generation of a potential called cochlear microphonic potential inside the celular body. A key concept is that these CMPs copies bioelectrically the frequency and intensity of the wave that activated the outer hair cell. This conversion from sound pressure waves to cochlear microphonic potential is analogic. After the CMP production, the outer hair cell transforms and converts the information contained inside the cochlear microphonic potential into short action potentials. These action potentials are sent to the brain through the spiral ganglia of the inner hair cells. This conversion from cochlear microphonic potential to bioelectric signal has been considered digital.

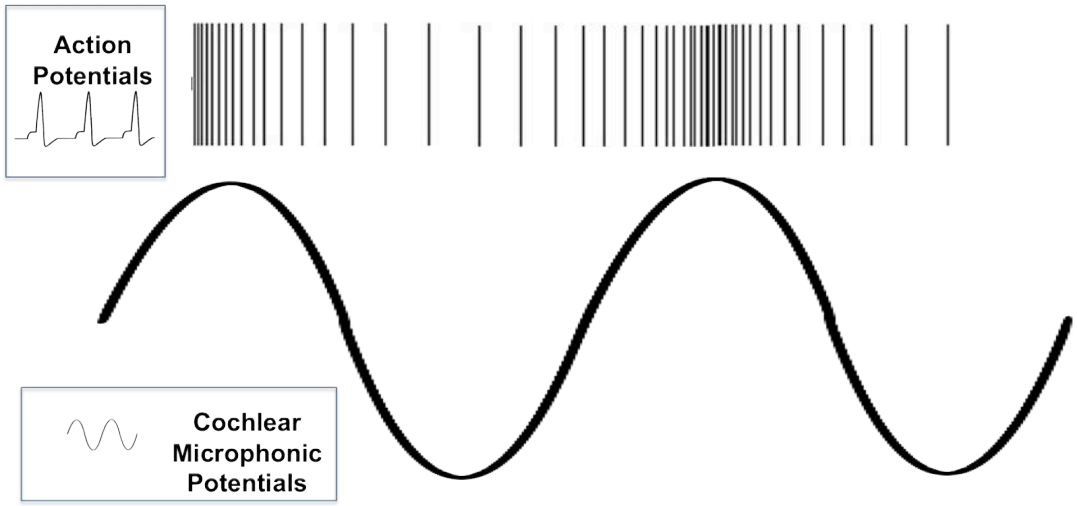

FIGURE 5: SCHEME OF CODIFICATION OF THE ACTION POTENTIALS FROM CMPS

In figure 5 it can be seen that the action potentials increase their frequency as a function of the cochlear microhonic potential amplitude.

Our project intends to focus on the CMPs and not in the signals that are sent to the brain. (Tortora G. J., 2009)

2.4.1 Brief historical review on CMPs

Through history, different theories of the bioelectric transduction inside inner ear have been changing and adapting to the new discoveries and technologies.

The French anatomist Guichard Joseph Duverney was one of the first pioneers in studying otology; in 1683, Duverney compared the cochlea as a set of resonance structures in his “Treatise on the organ of hearing, containing the structure, function, and diseases of all parts of the ear”. (Wikipedia "Guichard Joseph Duverney", 2016)

In 1918, Georg von Békésy established the theory of the resonance of the basilar membrane that is nowadays valid; Békésy published his first article related to the vibration pattern inside the cochlea in 1928. From that point on, he built mechanical cochlear models and developed the theory of the propagating waves for which Békésy received the Nobel prize in 1961. It can be also remarked the Békésy’s experiment with the stroboscopic light upon silver particles spread over the Reissner membrane; From this experiment he stated the travelling wave theory that it is still valid now. (Békésy, 1960) (NobelPrize.org, 2016)

In 1930, both the North-American psychologist Ernest Glen Weber and the English philosopher Charles Bray made a surprising finding. While working with *Felis Catus (*domesticated cats), they found that the auditive sensorial receptors (cochlear hair cells) produced potentials responding to the frequency of the sound stimuli. This response was similar to a conventional physical microphone. The name given to this potential observed in the hair cells was cochlear microphonic potential (CMP). Bray and Weber’s contribution increased interest as new possibility to apply it to human clinics. (Bray CW, 1930)(Weber EG, 1930). Bray and Weber also stated in 1937 the “Volley principle” that states that a group of neurons fire action potentials out of phase with respect each other when they respond to a sound; when the action potentials are combined a sound frequency of higher value can be encoded properly. ("Volley Theory" Wikipedia, 2016)

During the thirties decade of the twentieth century, several researchers dealt with this topic; around 1950, it was concluded that microphonic cochlear

potentials were useless due to technical difficulties for extracting this signals from subjects (Formm B, 1935)

In 1960 Johnstone and Boyle proved with reasearch animals that the movement of the basilar membrane was not enough to explain the frequency selectivity of the cochlea; after a lot of research, Johnstone and Boyle added to Békésy's theory the idea that the receptors along the basilar membrane acted actively in analogical frequency filtering processes. (Nuttall Alfred L, 2012)

From 1980 on, some controversy appeared between those who thought that the theory of active frequency selectivity along the basilar membrane was true (the cochlea played an active role in hearing) and the ones who thought that the cochlea was just a passive structure.

Nowadays, it has been added to Békésy's theory the idea that the receptors along the basilar membrane have bioelectric activity. Regarding the cochlea's anatomy, biochemistry and electrobiological behaviour a lot of reasearch has been done; nevertheless, how the information and signals are transduced through the cochlear structures is not clear yet. That is why the cochlear microphonic potentials may open a new door to fill up this knowledge gap and add new possible applications to hearing diagnostics in the clinic.

2.4.2 Conventional audiometry vs. cochlear microphonic potentials

Today, there are several ways to diagnose hearing losses in a subject, including audiometry tests, auditory brainstem response etc. Unfortunately, all audiometry tests are subjective, as they require the patient collaboration in order to identify hearing threshold levels. Regarding auditory brainstem potentials, they have considerably bigger amplitudes, in the order of microvolts. However this test is only useful if we want to know whether the signal arrives at that point or not.

On the other hand, the cochlear microphonic potentials have really small amplitude, in the order of nano-volts, but they proved to be useful because the following caracteristics are true when a pure tone wave (sinusoidal wave) of a given frequency and intensity is applied to the patient:

- The cochlear microphonic potential copies the frequency of the stimulating pure tone thanks to the microphone-like behaviour of the outer hair cells.
- The CMPs keep a phase relationship with respect to the pure tone.
- The CMPs increase their amplitude linearly with respect the sound pressure wave until it saturates and decreases again (in humans the linearity ceases close to the 90 dB due to the contraction of the stapedius muscle;

Regarding downsides of cochlear microphonic potentials, the following ones can be mentioned:

- CMPs have really small amplitude, in the order of nanovolts.
- The surrounding noise that interfere with the CMP (brain, heart, external noise to the subject, etc.
- If the test to be performed in adults, another drawback is that adults have thicker skin than children and therefore the impedance increase.
- Different species have different hearing system structures, thus the response changes significantly. In humans there are several factors that difference them from other species, such as the OHCs distribution along the basilar membrane, length of the OHCs microvilli, presence of the helicotrema elastic compensation of the round window (where the scala tympani ends) etc.

2.4.3 New concepts in CMPs

During 55 years Dr. Julio Sanjuan and his team were developing specific instrumentation for the bioelectrical study of the cochlea. Using CMPs, they achieved results about: latency of the outer hair cells, listening fatigue, masking, mechanical-electrical transduction and analogue digital transduction of the cochlear microphonic potentials that trigger the generation of evoked potentials.

LATENCY: Time that it takes since the pressure waves stimulate the outer hair cell microvilli until the CMP is produced

FATIGUE: When a subject is subjected for a long period of time to high intensity stimuli, cochlear function do not seem to be affected. The source of the fatigue is expected to be cortical.

MASKING: It is defined as the covering effect that external noise can exert on the outer hair cells when the noise has the same frequency component as the frequency of the outer hair cell.

MECHANO-ELECTRIC TRANSDUCTION: The cilia of the OHC vibrates at its biological frequency when there is no stimuli (this might be basic idea behind the outer hair cell function of biological filter). When the stimuli is applied, the cell depolarizes and the oscilation amplitude increases.

Thanks to the particular characteristics of the cochlear microphonic potentials it is possible to generate an objective audiometry test without the collaboration of the patient. The data obtained might help to fill an audiometric curve finding both the upper and lower hearing thresholds of a subject's audiogram. An audiogram is a graphic record produced by an audiometry, which is a measurement of the range (frequency) and sensitivity (intensity in dB) of a person's sense of hearing.

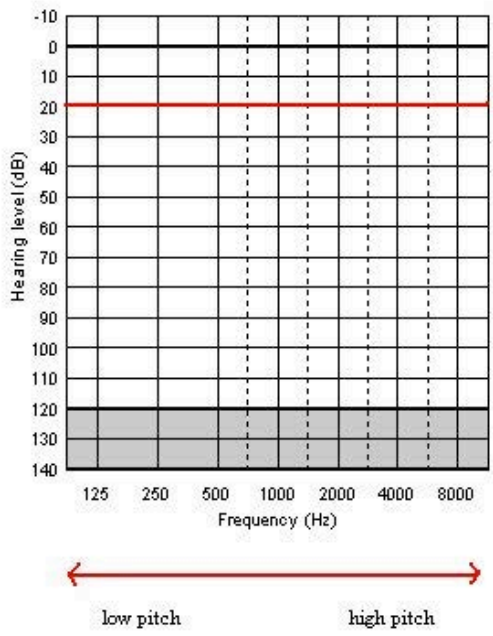

FIGURE 6: AUDIOGRAM (SOURCE: WIKIPEDIA "AUDIOGRAM")

2.4.4 CMP EQUIPMENT AND SAMPLEX SOFTWARE

Since 1990, Dr. Sanjuan and his research group at the Ramón y Cajal Hospital of Madrid have been investigating physiological parameters of the outer hair cells with a specific equipment for detecting cochlear microphonic potentials (MC/04) developed by the company "Electrónica General Española de Audiología S.L" (CIF:B78073608) and a software called SAMPLEX 1.1, developed by master's degree students from the Complutense University of Madrid in 1997. The main goal of this equipment is to describe visually (thanks to different graphs) the hearing loss of a subject from the auricle to the cochlea before the potentials are sent to the brain.

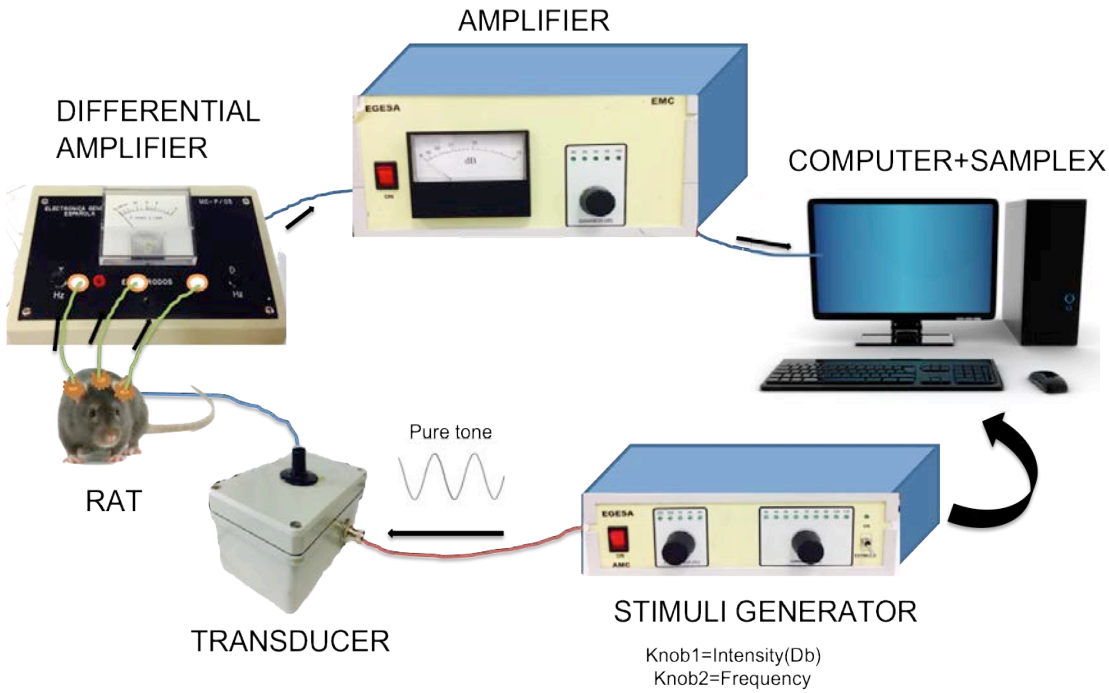

FIGURE 7: MC/04 CMP EQUIPMENT SET-UP

The equipment is divided into six main components (shown in figure 7): A **stimuli generator** of pure tones or sine waves with two knobs, one for selecting a frequency of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz, and another one for the intensity (in dB) between 30 dB and 110 dB. The stimuli generator also generates a square trigger signal sent directly to the computer and therefore syncronizing the original stimuli and the signal recorded. A **transducer** that turns the electric sine waves into sound preasure waves. Those sound pressure waves are collected through a plastic tube that ends up in an olive shaped electrode placed inside the auricle of the subject. The

transducer is shielded to avoid external noise to interfere in the signal. In the **subject**, three electrodes are placed: one on the mastoid bone behind the left auricle, another one on the mastoid bone behind the right auricle and the last one (ground) in the forehead. The impedance between electrodes and skin must be lower than 7000 Ohms; in order to reduce the impedance for the signal a paste made of sodium chloride and lauryl alcohol (dodecanol) is placed beween the skin and the electrode. The signal that comes out from these electrodes contains the cochlear microphonic potentials. The cables of the electrode go to a **differential amplifier** to reject common mode noise: the gain of the differential amplifier is about 45 dB. The fifth component is another **amplifier** with narrow pass band analogic filters tuned for each one of the possible frequencies that can be selected in the stimuli generator. The gain of this amplifier is of 120 dB. The signal that comes out from the amplifier it is supposed to have one single frequency. However, that signal also carries undesired noise at that specific frequency, coming from external perturbations, or from the equipment itself (an unavoidable source of noise is the stimuli generator), as well as internal noise of the subject's internal structures. This it is why the signal is post-processed in a **PC** with the software SAMPLEX 1.1, to minimize the effect of the noise thus detecting the cochlear microphonic potentials.

SAMPLEX 1.1 was created for a specific Windows version, Windows XP 32 bits with the .net 3.5.

The functions of this programe are:

- Averaging the signal coming from the amplifier.
- Substracting the noise component of the signal (previously acquired with the stimuli generator off) from the signal containing the CMPs (this process has to be done for each frequency)
- Configuring a worklist of patients
- Ploting graphs of recruitment and two audiograms with its audiometric curve, one for each ear.

Nevertheless, the SAMPLEX software has several drawbacks that make it inefficient nowadays: In order to install the software we need an specific version of Windows XP and a .net file that are no longer maintained, the

programe also requires components such as parallel ports and PCMCIA cards, and it requires callibration every time the PCM components are set. (Sanjuán Juaristi, Conventional audiometry versus cochlear microphone audiometry, 2007)

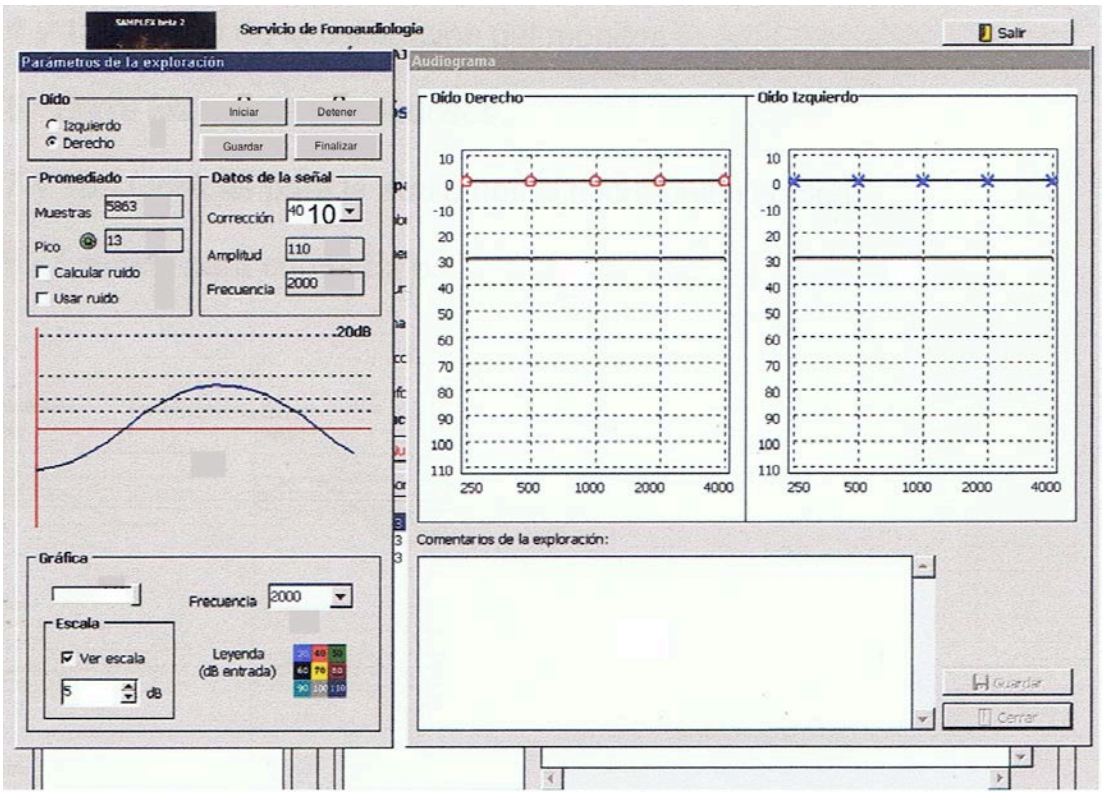

FIGURE 8: INTERFACE SAMPLEX 1.1 SOFTWARE

“The biggest risk is not taking any risk…In a world that changing really quickly, the only strategy that is guaranteed to fail is not taking risks”

Mark Zuckerberg

3

SOCIO-ECONOMIC AND LEGAL FEASIBILITY

3.1 Market analysis

The brief market analysis in this bachelor thesis is intended to be é an market pre-evaluation before a definitive analysis is carried out. The importance of creating a reliable market analysis for the inventor and its partners is essential, it may lead to protect the invenction properly, provide an overall vision of the field, further develop the resulting products or services and find reliable sources of funding.

3.1.1 External analysis

Hearing loss or hearing impairment is just the inability of a subject to hear properly.There are several factors that contribute to the loss of the the hearing function such as age (also known as presbyacusis (the older the subject, the greater the degeneration of sensory cells will be), noise (the louder the noise, the more damage), diseases (there is a long list of deseases and drugs that cause the hearing system to fade: acoustic trauma, otitis media, otosclerosis and antibiotics, respectively, etc.), genes (spontaneous gene mutations afterbirth or inherited defective genes from the parents can

cause the wrong phenotype to be expressed) and dementia (due to brain misconections or neuronal deterioration). (hear-it.org, 2016)

In 2015, the World Health Organization stated that there were around 360 million people in the world that suffered from hearing loss, which corresponds to 5% of the total worldwide population. Out of those 360, 32 million are children with a loss of 30 dB or more. (WHO, 2015)
As far as Spain is concerned, 163.627 people between 0 and 80 years old with a certified auditive disability greater than 33% were registered in the "Base Estatal de datos de personas con valoración del grado de discapacidad" in December 31st 2014.(IMSERSO, 2015)

People seeking for a solution to their auditive problems in Spain can apply for help to the National Health system or to a private hearing health care professionals so as to obtain audiometric check-ups, hearing aids, cochlear implants surgery, etc. Unfortunately, Spanish health care system does not cover the cost of both the maintenance (up to 300 euros for a defective wire) and batteries (up to 1400 euros if the battery runs out of autonomy) (Luis, 2015)
When it is noticed by the subject that something does not work as it should inside the auditive system, there exist several technical possibilities to tackle it.

The are three types of possible devices applicable: 1) diagnostic devices (audiometers, auditory brainstem response analyzers, otoacoustic emissions analyzers, otoscopes and tympanometers), 2) hearing aid devices (analog, digital signal processing) and 3) hearing implants (bone anchored, cochlear and middle ear). (GLOBAL DATA, 2016)

According to the WHO, half of all cases of hearing loss are avoidable through primary prevention, as it is the case of audiometry proccedures.

3.1.2 Business proposal and value proposition

On June 6th 2015, Dr Julio Sanjuan Juaristi brought his prototype equipment (described in section 2.4.4) of objective audiometer based on cochlear microphonic potentials (CMPs). Dr. Sanjuan and his partner, Carlos Conejero, have a company in common called Zero Entropy S.L. This company was interested in collaborating with the "Laboratorio de Imagen Médica" of the Gregorio Marañón hospital in Madrid and the Carlos III University of Madrid. The goal of this partnership is to study the commercial and technical feasibility of re-implementing the CMPs equipment using modern and digital technology.

The value proposition is a short statement, normally a paragraph that should clearly answer three main questions; who is the customer?, what is it going to be sold? And what value is being provided to the customer(s)?.
The value proposition would be:
"*The partnership is intended to assess the feasibility of an objective and non-invasive audiometry system for both clinic (adults and newborns) and scientific reaserch users so as to understand the cochlear physiology and help physicians to diagnose auditive defects in patients*".

The advantages of the audiometry system proposed are that it is:

- Objective → The audiometry test do not requiere the collaboration of the subject of study.
- Non-invasive → The audiometry test will be non-invesive for humans with the placement of three electrodes: two behind the ear auricle and one for ground in the forehead. However, for animal research the test may be invasive.
- Selective and independent → It is possible to select the range of frequencies to be studied in the subjects. This test results are independent from other medical test and give reliable data.
- Personalised → Determination of the auditive area and both the superior and inferior threshold, graphically.

During several meetings hold in the Gregorio Marañón Hospital regarding the CMP audiometer project, the role distribution of the tasks and activities that each member of the partnership should do was established. Particularly, our role in the IisGM is to develop a software prototype for testing it in a cochlear microphonic potential equipment. Money-wise, the amount of funds needed to develop the new hardware equipment described in CHAPTER 4, the market analysis, business plant, crew, intellectual property rights and software it is estimated to be around one million euros. That is why a funding source must be found.

3.1.3 Feasibility study

3.1.3.1 Databases consulted

3.1.3.1.1 Global data

Global Data (GB) is a database website whose main goals are gathering data (from conferences, companies, patent databases, universities, tech transfers, press releases and startups), modeling and forecasting the previous mentioned data, updating as much information in the website as possible in real time (Global Data relies on companies or universities updates schedulling times) and finally it provides a critical market analysis and recommendations to clients according to the expertise of PHDs, Physicians, etc.

GB offers its customers extensive information on pipeline products in various stages of development that cover from the discovery and clinical trials to the launch to the market.

Global Data has several sections, the one used in this work is Global Data Healthcare and in particular Global Data Medical.

The market analysis can be done over devices belonging to several medical sectors such as cardiovascular, diabetes care, general surgery, neurology, wound care management, among other fields. As this bachelor thesis is focused on the hearing system, the area is ENT (ear, nose, throat) diagnostic devices which are the ones used to evaluate the hearing ability of a subject. The device that matters is the audiometer. Within Global Data Market analysis

tool we have to also select the data type (value, volume and company), select the years in order to see the evolution of the data and finally the currency that it is going to be used in the analysis**.** (GLOBAL DATA, 2016)

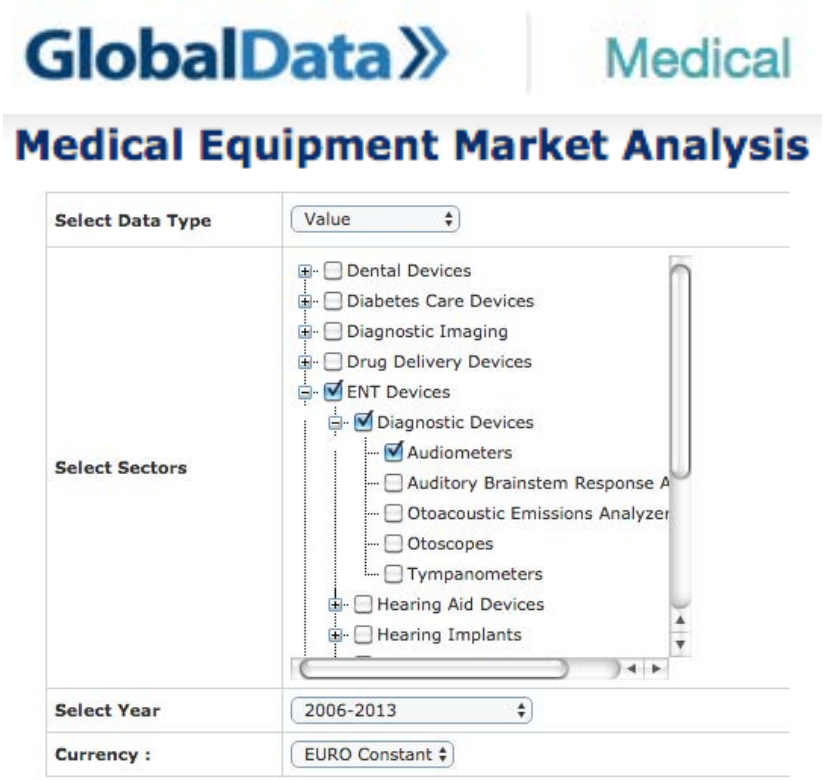

FIGURE 10: SCREEN-SHOT OF GLOBAL DATA ANALYSIS

Once the predefined Global Data queries were selected, results regarding market size such as volume of the audiometer market and millions of euros that the audiometer market moves are both obtained.

VOLUME IN ABSOLUTE UNITS OF AUDIOMETERS (Global Data, 2016)					
Market	**Region/Country**	**2013**	**2014**	**2015**	**2016 (expected)**
Audiometers	North America	12648	13242	13862	14513
	Europe	7227	7531	7849	8177
	Spain	1402	1461	1523	1587

TABLE 1

MILLION EUROS AUDIOMETER MARKET (Global Data, 2016)					
Market	**Region/Country**	**2013**	**2014**	**2015**	**2016 (expected)**
Audiometers	North America	65.1	67.5	70.0	72.5
	Europe	28.6	29.5	30.3	31.2
	Spain	3.8	3.9	4.1	4.2

TABLE 2

This data shows that the audiometer needs increases in North America and in Europe and it is greater in North America.

Searching on Global Data, some potential areas of application in which partners, customers or competence can be found are the following ones:

a. Service of otorhinolaryngology in hospitals (both public and private) for performing audiological studies.
b. Service of neonatology in hospitals for performing audiological studies to newborns.
c. Reasearch centers such as the IiSGM or universities, for investigating on hearing physiology.
d. Companies related to the hearing field. In Global Data some interesting companies are showing active activity in this field, this makes them possible future partners to the project. In table 3 a brief summary of some companies and its products are provided.

COMPANY	PRODUCTS
AMPLIVOX (http://www.amplivox.ltd.uk/)	•Audiometry accesories •Power supplies •PC connectivity options •350S Acoustic Booth for audiometry tests
MAICO DIAGNOSTICS	•Audiometers (Screening,

(http://www.maico-diagnostics.com/)	diagnostic, PC) •Middle ear analyzers
INTERACOUSTICS (http://www.interacoustics.com/)	•Evoked potential analyzers •Audiometers

TABLE 3

3.1.3.2 INTELECTUAL PROPERTY RIGHTS

According to the prestigious economist Joseph Alois Shumpeter, Intellectual Property rights (IPR) can be described in the following way: "Whenever a company develops a valuable innovation, it can appropriate a large share of the value created, since it enjoys a temporary monopoly position". Nevertheless, this monopoly disappears with time and becomes worthless due to imitation, changes in the market or just the product or service becomes obsolete.

The value and benefits that the owner get will increase as long as they have clear the four main components that drive the innovator's advantage:

a) Define what is the type of property right according to the nature of the innovation: Patents → products, processes, substances or designs; Copyrights → exclusive production of the author(s)' artistic, literary, dramatic or musical works; Trademarks → word, symbols or other marks to distinguish a brand or other goods or services; and Trade secrets → customer lists processes, formulae, recipes and knowledge assets.
b) The knowlege of an invention has to be classified in explicit if the knowlege can be written down, or tacit if the knowledge is transmitted orally.The intangible assets of a company are potential sources of benefits if they are identified and evaluated properly. The knowledge has to be classified also into simple or complex.
c) Lead time that is the opportunity period of time that has the leader (or innovator) over the followers.

d) Having complementrary resources such as finance expertise, profitable production and reliable suppliers, customers and partners. (López, "IPR", 2016)

In this project the physical hardare should be patented and the software has to undergo a copyright protection. Now it is important to understand what a patent is, its requirements and it is also advisable to know when an invention should not be patented.

A patent is a document that certifies that someone has two main rights over a specific invention, exclusion and explotation. The former means that the patent owner can exclude third parties from using, reproducing, importing or selling; the latter means that the patent owner can use the invention in all the possible ways while others do not.

In order to get a patent the invention must fulfill three requirements: The invention must be new, involving an inventive step that may lead to an industrial applications. There exist a list of things that cannot be considered as an invention and therefore cannot get the patent, some of them are: scientific discoveries, theories or mathematical methods; plans, rules and methods for exercising imtellectual activities, games or business activities; formats for delivering and communicating information. Surgical proccedures and techniques, diagnostic methods and therapies are not patentable under the Spanish patent law due to the fact they lack the industrial application requirement, however, products, machines and medical equipment are allowed to be patented; any human body part or gene sequences (which has not been created artificially); plant and animal varieties and all possible biological processes for the production of animals or plants; and last but not least, one of the biggest mistakes that an inventor should never make is publishing or mentioning in any kind of format crucial data that is going to be included in a patent.

Finally, who may benefit from the patent apart from the inventor?. Exceptionally the inventor’s partner or employees if the inventor agrees and the heirs. In the case of universities, the university is the one that holds the right from any kind of faculty reasearch performed on its associated facilities. (López, "Patents", 2016)

Several years ago Dr. Sanjuan tried to patent his equipment for the detection of the cochlear microphonic pontentials (CMP), nevertheless, the board in charge of evaluating this patentability process rejected the patent application form. The reason was that during his career, Dr. Sanjuan mentioned and described key concepts that were the core of the patent in countless lectures, congresses, informal talks and disparate publications.

Actually, since 1961, Dr. Julio Sanjuan has been publishing articles and publications related to the cochlear microphonic potentials. Some examples are: “Potenciales cocleares y trauma acústico” (1967), “Nueva técnica de diagnóstico precoz de la sordera” (1989), “Estudio de la audición en prematuros” (1997), “Actividad funcional de las células ciliadas externas” (2008), “Fatiga auditiva” (2013), “Latencia de los microfónicos cocleares” (2014).

The only possible solution was to find partners such as universities and innovation groups in order to develop new characteristics for the CMP equipment that would result in a new patent.

For the same reasons, it is not possible to include in this bachelor thesis further expansions about future possible patents. Just to say that the process is still under analysis.

3.1.3.3 Regulation and law

Medical devices are all of those that are used in the medical facilities and are regulated by the European directives 90/385/CEE, 93/42/CEE and 98/79/CE for active implantable products, general products and diagnostic in-vitro products respectively. (AEMPS, 2014).

All these medical devices must bring the so-called CE marking, which is a symbol that is placed on top of the device for showing that a product fulfills all the requirements of both legal and physical safety inside the European Economic Area. In United States, the equivalent to CE marking is called FCC Declaration of Conformity. (“CE marking” Wikipedia, 2016)

Inside the European Union, Spain has the “Real Decreto” 414/1996, March 1st, which regulates manufacture, import, certification, put into the market and service, distribution and advertising of an specific medical product.

Depending on the potential risks that the medical product may bring, it has been established a classification from less to higher risk: I, IIa, IIb and III. In the Annex IX of the "Real Decreto" 1591/2009 of October 16th the classification is done according to the criteria described. The following table shows several examples of each class. (BOE, 2009)

Classification Medical devices			
Class I (low risk)	Class IIa (medium risk)	Class IIb (medium risk)	Class III (high risk)
Bandaging	Audiometer	Dental implants	Endoprothesis
Crutches	Ultrasound instr.	Blood bags	Coronary stents
Surgical Beds	Contact lenses	Anasthetic devices	Breast implants
Medical instr.	Muscle stimulation	X-Ray	Heart valves
Wheel chair	Tooth filler and crowns	Dyalisis devices	Breast implants
		Condoms	

Table 4 (MedCert, 2015)

As it can be seen in the table 4, the audiometer would be class IIa, and as such it requires several tests and trials to be performed before applying for the CE marking. According to consulting companies, the estimated cost of the process may easily reach 80,000 euros.

3.1.3.4 Search of economic resources (funding)

Every technological project needs funds, they are the core of a business; money is essential for writing a formal market analysis, developing the reasearch, taking on people to collaborate in the project, buying the things that are necessary and last but not least paying all the taxes. A good market analysis is estimated to cost between one thousand euros to hundred thousand euros, depending on its complexity and how many details are covered. The more fields are included into the market analysis, the better.

The areas for which we are pursuing funding are: taking on more employees to collaborate in the project, writing a complete and detailed market analysis document, developing a new proof of concept of the device along with a new software programme for the new device, finding money for all the intellectual property rights matters.

Several possible funding sources are presented below.

3.1.3.4.1 FIPSE

FIPSE is the “Fundación para la Innovación y la Prospectiva en Salud en España”. FIPSE has implemented a programme called “Programa de apoyo a la innovación en salud” whose aim is to provide funds for the structuration of scientific reasearch projects in order to increase their potential to be transfered into the market and promoting their innovation and the project application into the industry. This fund programe is divided into three stages:

- Feasibility studies. The funds are given for the intellectual property rights, titularity, scientific and technogical feasibiity to check if the project is feasible, economic feasibility study for developing a business plan and developing a commercialization plan. The amount given if all the requirements are fulfilled is 50,000 euros.
- Proof of concept. Once the feasibility studies are done, a proof of concept of the device should be developed stating clearly when it is going to be ready and how much money is going to cost every step and component.
- Transfering the technology into the industry. The funds are destinated to the companies that have everything prepared to transfer their technology to the market.

In the case the funds are given to the company, FIPSE will contribute actively in the development, exploitation and diffusion of the technology generated.

The project of the audiometer can be intended to received funds from the first FIPSE stage as the Cochlear Microphonic hardware and its software are defined as a medical diagnostic device whose conceptual development is already clear. (FIPSE, 2015)

3.1.3.4.2 La caixa

La Caixa is a Spanish bank that funds several social fields. One of them is the scientific research and support to scientific startups. An example of the instruments for funding that La Caixa (in collaboration with the Centro de Desarrollo Tecnológico Industrial) created was “Caixa Innvierte Start”. This funds contain around 20 million euros for beggining startups in “fase semilla”. (Gozzer, 2016)

The main drawback of this funding option is that the bank has very strict rules about the follow-up of the companies progresses, and about the deadline dates when the results should be ready.

3.1.3.4.3 European SME instrument

The SME (Small and Medium Enterprise) instrument receives funds from the Horizon2020 project. The main goal of this instrument is fostering a company in the market improving the business plan of an innovative technological product. Entities that could apply to these funds are SMEs with a radically innovative idea that wants create value inside the Europea Union growing a business. In our case, it could be the company “Zero Entropy S.L” with the possibility to subcontract the IiSGM.

The SME instrument has three different and independent stages of funding: Stage I, stage II and stage III. Stage I is the one that we are interested in; it consists on 50,000 euros for developing a strong business model in which the feasibility of the proposed technological product must be covered and additionally coaching support.

The applicant (Zero Entropy) should provide a ten-page document describing its proficiency in some of the following competences:

- Clearly describing an existing problem in the market and proposing a detailed value proposition in order to solve the problem.
- Designing a commercialization scheme showing the expected sources of income. Furthermore, all the mechanisms of intellectual property rights that are wanted to be applied over the Cochlear Microphonic potential device must be included. This step in the document is very important when evaluated by the board.

- A list of costs, and the activities performed between the company and subcontracted partners must be included.
- A decription of the partnerships that are going to be carried out and the role of each each entity.

For these funds there are several calls for stages I and II, which are in March, June, September and December.

The SME instrument Stage I is the ideal source of funds to this project due to the fact that it may help in developing a good proof of concept, including: proving the technical and commercial viability, explore the regime of intellectual properties, designing a study, develop a pilot application and a risk assesment study. (European Commision, 2016)

3.1.3.5 Budget estimation

Once the source of incomes has been selected, in this case the European SMEs (Small and Medium-sized enterprises) funds, the costs of this project feasibility study must be found. The amount of incomes would be 50,000 euros.

The budget estimation is the amount of money needed for a specific purpose. Estimating the income and expenditure of a project is really important for making a successful business. In table 5 the estimated costs for the CMP system feasibility study are shown.

Areas	Recipient		Total (Euros)
Advice and management	Technical and commercial viability		1500
	Business model		1000
	Advisory		1000
	Market study and risk assesment		1000
	IPR	Freedom to operate document	3000
		Patentability document	2000
		Patent application	2500
	Software	Matlab standard license	2000
		Matlab signal processing toolbox	1000

Prototype development	Hardware	New differential amplifier	1000
		PC	500
		Transducer	100
		Tubes, electrodes,cables	100
	Technical validation		2000
	Salary x1 engineer (40euros/hour; 4hours/day; 4days/week; 4weeks/month; 6months)		15360
			32260

TABLE 5

3.2 CONCLUSIONS ON MARKET STUDY

The objective audiometry (plotting the audiogram of a patient) based on CMPs is an innovative idea that seems to be feasible, however a way to protect the inventions is advisable, a patent for the CMP equipment and copyright for the software. Provisions have to be made regarding CE-marking before the development is finished. Regarding funding, the most reasonable funding option is Stage I of the SME instrument whose duration are 6 months.

“First, solve the problem.
Then, write the code”

John Johnson

4

IMPLEMENTATION

4.1 System design

During June 2015, Dr. Julio Sanjuan (along with his partner, the company “Zero Entropy”) brought the equipment mentioned in figure 11 to the IiSGM so as to begin a partnership regarding its equipment functionality. One of the biggest downsides of that device is that it makes use of components that are no longer common in electronics such as the parallel ports, PCMCIA cards, equipment built in 90’s decade of the XX century, etc. One of the goals of this bachelor thesis is to provide an alternative scheme to Dr. Sanjuan’s proposal in order to make it more modern and reducing the amount of hardware used. From October 2015 to March 2016 several meetings were hold at the Gregorio Marañón Hospital so as to decide different scheme proposals and to describe the partnership responsabilities regarding the PMC project. The author of this thesis contributed by assisting to the meetings and writing the minutes of the meeting documents.

The new scheme proposed by the IiSGM team formed by the author of this bachelor thesis and his advisor, is shown in figure 12.

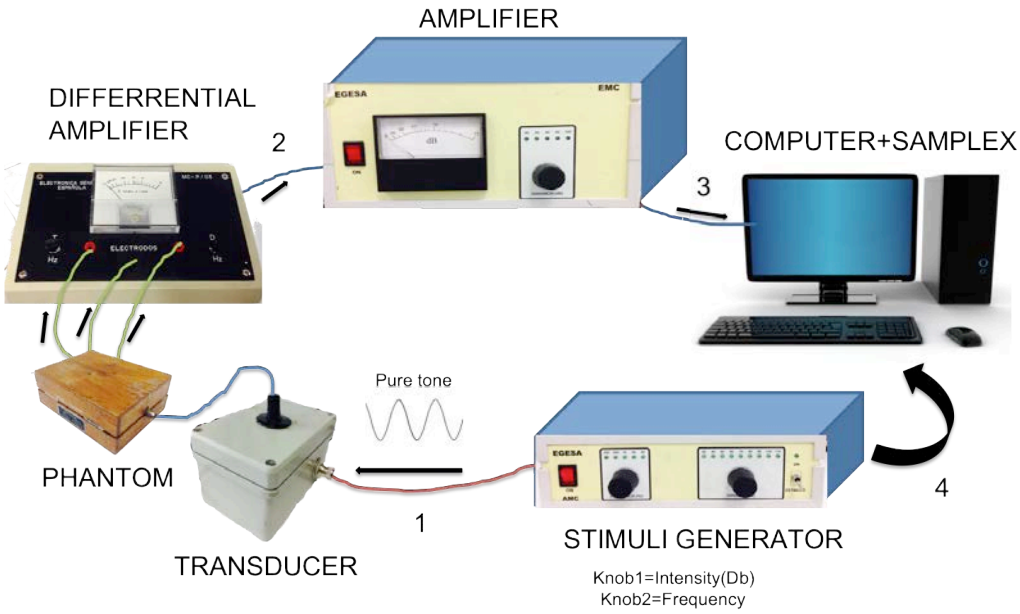

FIGURE 11: DR. SANJUAN'S SETUP

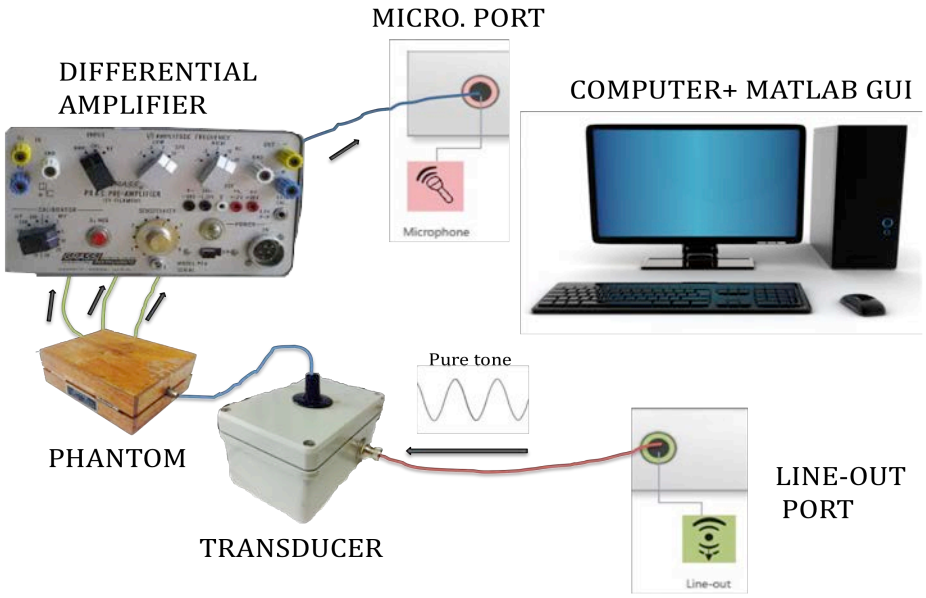

FIGURE 12: IISGM SETUP

In few words, what we have changed with respect Dr. Sanjuan equipment is getting rid of the stimuli generator and the amplifier with filters; Both of them have been replaced by a Matlab script with a graphical user interface GUI (generating, receiving and digitally filtering the signal). Besides we have substituted the old differential amplifier with a modern high-performance GRASS differential amplifier. The phantom and the loudspeaker were kept.

4.2 Hardware implementation

4.2.1 System characterization

For three months all the equipment in figure 11 was set in the LIM ("Laboratorio de Imagen Médica" of the Gregorio Marañón Hospital of Madrid) facilities, and the signals from different points of the circuit were checked in order to know how the original PMC system worked. This signal testing process coincided with the internship (from June 2015 to August 2015) of the author of this thesis in the IiSGM.

In point 1 of figure 11, a sinusoidal wave was measured with an oscilloscope DS1104B RIGOL for all frequencies and intensities allowed in Dr. Sanjuan's stimuli generator.

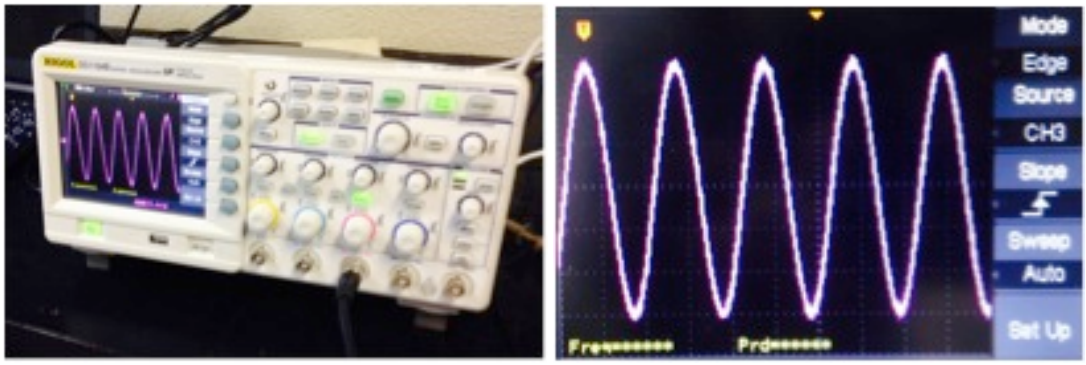

Figure 13: signal of point 1 figure 11, shown in the oscilloscope

The following table shows the voltages peak to peak (V_{pp}) for every intensity and frequency of the stimuli generator (oscilloscope probe in point 1 of figure 11) are shown.

[dB] / [Hz]	30	40	50	60	70	80	90	100	110
250	24mV	32mV	64mV	176mV	528-560mV	1.6 V	5.2V	8V	10V
500	40mV	40mV	40mV	80mV	120-160mV	320mV	1V	2V	2V
1000	77.6mV	77.6mV	77.6mV	77.6mV	77.6-160mV	155-240mV	388-466mV	698-800mV	698mV
2000	77.6mV	77.6mV	77.6mV	77.6mV	77.6mV	155mV	388-466mV	698mV	698mV
4000	77.6mV	77.6mV	77.6-155mV	155-233mV	543mV	1.5V	5.1V	9.8V	10V

Table 6: V_{PP} as a function of frequency and intensity

The computer used for recording the signals was a DELL OPTIPLEX GX620 with the following specifications: Windows XP version of 32 bits and the 3.5 .net; a line-in port; parallel port or PCMCIA port. Additionally, the software “Audacity 2.0” recorded the signals and saved them in .wav files. The software Audacity is a free, open source, cross-platform software for recording and editing sounds. (Audacity, 2016)

For measuring the signal from point 2 of the figure 11, we used the following components to connect the differential amplifier and the computer: BNC (male) to RCA (male) cable, a RCA (female) to RCA (female) cable and a RCA (male) to a stereo jack connector cable.

For measuring the signal from point 4 of the figure 11 (a squared signal), we used the following components so as to connect the stimuli generator and the computer: RCA (male) to jack cable.

These signals from point 2 and 4 were simultaneously recorded and saved with the Audacity software in the same .wav format, taking advantage from the stereo property.

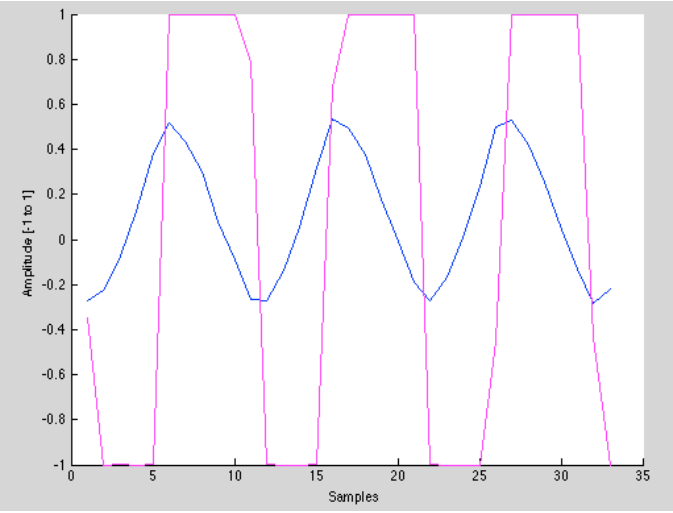

FIGURE 14: SIGNAL AT POINT 2 FIGURE 11 (BLUE) OF 4000HZ AND 80 DB, AND SQUARED TRIGGER SIGNAL AT POINT 4 (PINK)

In order to measure the maximum voltage in the audio output from the DELL model latitude x300 laptop, we connected the oscilloscope and set the audio at the highest volume. The maximum voltage peak to peak of 476 mV was reached. In the table 7 the voltages peak to peak (V_{pp}) for some

intensities and for some frequencies of the Dr. Sanjuan's stimuli generator (oscilloscope probe in point 2 of figure 11) are shown. The hyphen means that we observed saturation on the oscilloscope; in green are the voltages that were detectable by the user in the oscilloscope screen.

[dB] / [Hz]	30	40	50	60	70	80	90	100	110
250	24mV	34mV	84mV	176mV	-	-	-	-	-
500	40mV	40mV	40mV	90mV	156mV	324mV	-	-	-
1000	20mV	40mV	76mV	104mV	160mV	230mV	464mV	-	-
2000	40mV	72mV	76mV	80mV	100mV	155mV	464mV	-	-
4000	88mV	112mV	155mV	233mV	-	-	-	-	-

TABLE 7: V_{PP} AS A FUNCTION OF FREQUENCY AND INTENSITY

4.2.2 IISGM CMP SETTING

As it was mentioned before, the proposal of the IiSGM group is shown in figure 12. The new setup is formed by the following hardware (in bold):

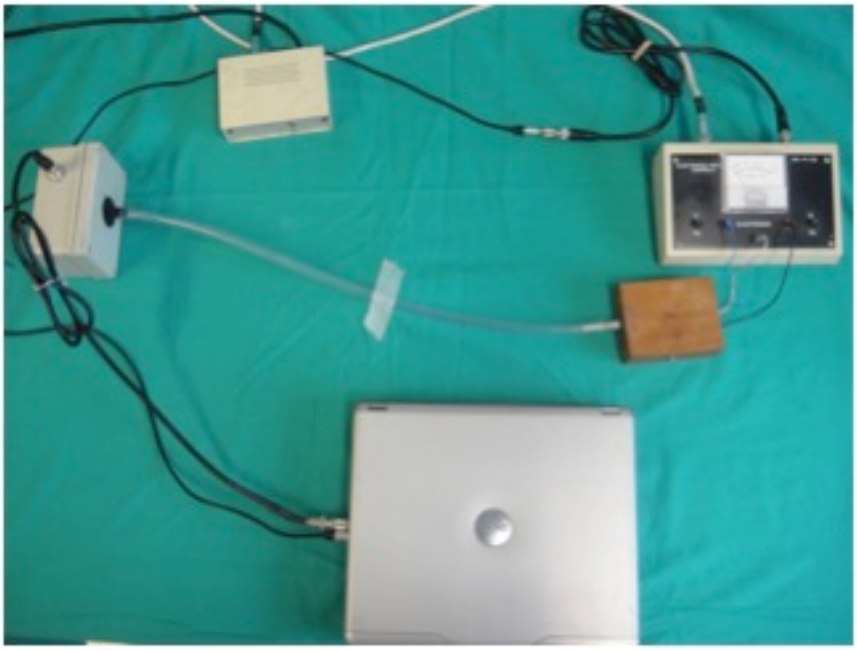

FIGURE 15: IISGM SETUP

PC computer (DELL model latitude x300 laptop). The pure tone signal generated in a specific MATLAB script (described in 4.3.3) is sent out through the line-out port, and after passing all the circuit and the subject it returns to the computer through the the microphone port and afterwards it is processed with the MATLAB script.

FIGURE 16: MICROPHONE PORT (LEFT), LINE-OUT PORT (RIGHT)

A computer converts an analog signal into digital by discretizing the signal. This process is called quantization.

The sound card of the computer should be set at least to 32 bits of bit depth (the sample size in digital domain) and a sampling rate (rate of capture) greater or equal to 44100 Hz. If the bit depth is 8 bits we could have 2^8 (256) values, thus applying the dB formula it could only span 48 dB (dB=20*log(256/1)=48 dB). If the bit depth is 16 bits we have 2^{16} (65536) values, thus applying the dB formula the new range is 96 dB (dB=20*log(65536/1)=96 dB). If the bit depth is 32 bits we have 2^{32} (4294967296) values, that translate into 192 dB (dB=20*log(42949672966/1)=192 dB). The higher the bit depth, the higher the dynamic range and the greater the signal detail we will be able to detect. Regarding sampling frequency, the Nyquist theorem states that for reconstructing a signal of an specific bandwidth, in this case for the audible sound, the sampling frequency must be greater than twice the highest frequency of the signal sampled. If we have a sampling frequency of 44100

Hz means that it would be possible to detect signals with a frequency of 22050 Hz or less.

It is also important to consider the concept that humans need to communicate and therefore they need to have more sensitivity in the range of voice frequency which ranges between 300 Hz and 3200 Hz.

A shielded **transducer** that converts the electric sine wave generated in the PC into sound waves.

A **plastic tube** to collect the sound waves towards the phantom.

A **phantom** that simulates the microphones of the outer hair cells. It may be built in two ways. The first one is a box containing a microphone and an attenuator, connected to three electrodes that go to the differential amplifier. The second option is sticking a microphone into a potato; the potato will act as the “head” of the subject attenuating the sound waves and providing us with a more realistic response. In order to register the signal we have to place three electrodes in the potato; these electrodes can act as a potentiometer, if the three pins are touching each other there will be no signal, whereas if the pins are further apart we will have more signal.

FIGURE 17: BOX PHANTOM

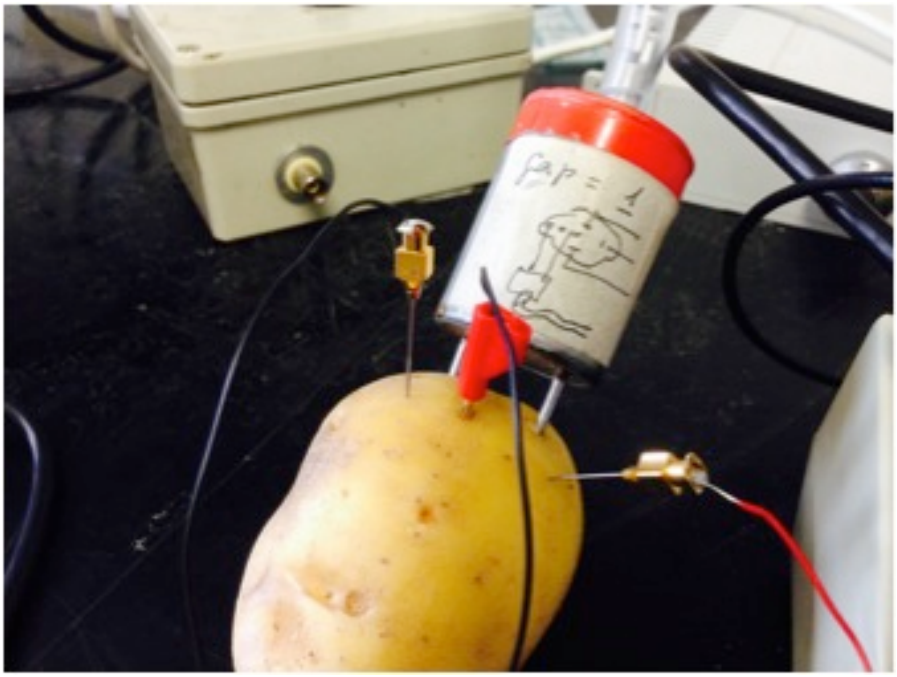

FIGURE 18: POTATO PHANTOM

The next component is a **differential amplifier**. For this project we used two devices: Dr. Sanjuan's differential amplifier (the circuits cannot be shown) and the GRASS AC pre-amplifier model CP511. The specifications from the GRASS differential amplifier are:

- AMPLIFICATION
    - Amplification: 15 minimum to 200000 maximum.
    - Amplification settings: 6-position step switch. Settings of 5, 10, 20, 50, 100 and 200; And two-position switch, X10 and X1000.
    - Vernier control: Attenuates amplification settings 3 times.
- FILTERS
    - Low pass filter: 2-pole (-12 dB/octave): 0.01, 0.1, 0.3, 1, 3, 10, 30, 100 and 300 Hz.
    - High pass filter: 4-pole (-24 dB/octave): 0.03, 0.1, 0.3, 1, 3 and 10 kHz.
    - Line filter: Notch-type filter (50/60 Hz), switch selectable.

- INPUT CHARACTERISTICS

- Input impedance: 20 megohm, differential, 35 pF at connector per terminal.
- CMR (Common-Mode Rejection): Adjustable to 30000:1 (90 dB) at 60 Hz.
- Noise: 4 microvolts peak to peak, referred to input, inputs shorted, 3 kHz bandwidth.

- OUTPUT
  - Type: Single-ended, clipped at approximately 10 V, peak to peak.
  - Output impedance: 500 ohms.
  - Output DC level: Adjustable to zero.
  - Terminals: BNC front and rear panel.
  - Trace restorer: Push-button control to return output to 0 V.
- CALIBRATOR
  - Range: 12 values from 10 microvolts to 50 mV in 1, 2, 5 steps; +/- 2% accuracy.
  - Internal calibration: Pushbutton actuated, DC voltages.
- PHYSICAL SIZE
  - CP511, ICP511: 21.9 cm x 8.9 cm x 21.6 cm
    - Weight: 1.2 Kg.
    - To rackmount: order kit CPRK1 for a single amplifier, or CPRK2 for mounting two amplifier side by side.
  - P511, IP511: 48.3 cm x 8.9 cm x 21 cm.
    - Weight: 1.3 Kg.
- REGULATORY
  - ETL listed to UL2601.1 and CSA 22.2 #601.1
  - CE marked to MDD 93/42/EEC

4.3 Software implementation

The core of our proof of concept scheme is a MATLAB script with its own graphical user interface (GUI). The MATLAB version used to write the code is R2012a. The computer that has been used is a MacBook Pro (Processor: 2.53 GHz Intel Core 2 Duo. Memory: 4GB 1067 MHz DDR3).

In the following three subsections the appearance of the GUI, the main script functions and the code are described.

4.3.1 Matlab script functions

- Generating a pure tone wave with both frequency and intensity parameters selected by the user, and with a specific time.
- Generating a trigger signal at the same frequency and phase that the pure tone.
- Show the single wave period corresponding to the average of all the sine waves periods.
- Display the recorded signal after going through the CMP setup of figure 12 and the subject.
- Display the pwelch spectrum of the recorded signal.
- Display the filtered signal.

4.3.2 GUI description

A GUI is visual way for the user of interacting with a computer using items such as windows, icons, menus etc.

The first step, before writing the code, was to sketch a drawing of the desired interface, including the main features and buttons. In the GUI, the buttons should be arranged in different areas of the screen according to their function and the general disposition of the other elements should be as intuitive as possible to the user.

The final MATLAB GUI may slightly change with respect the sketch design, however the main distribution should be kept.

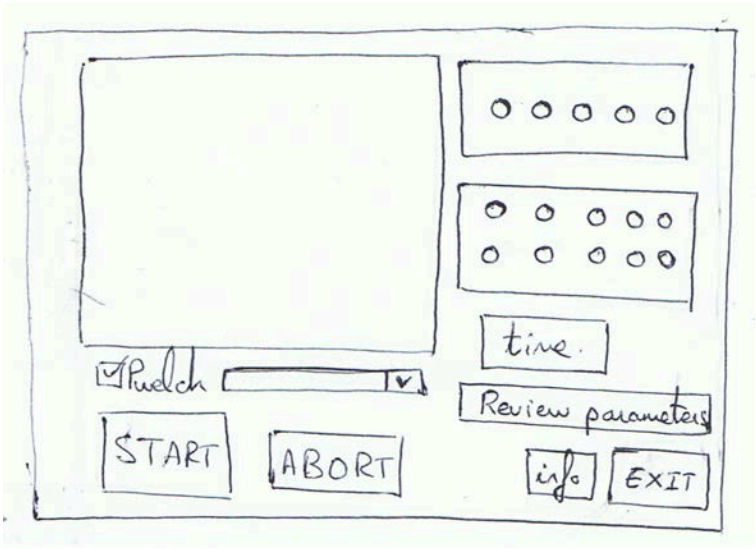

FIGURE 19: SKETCH GUI

When the final sketch has been drawn, the programmer opens the MATLAB GUI desing window and starts including the desired elements in the working window.

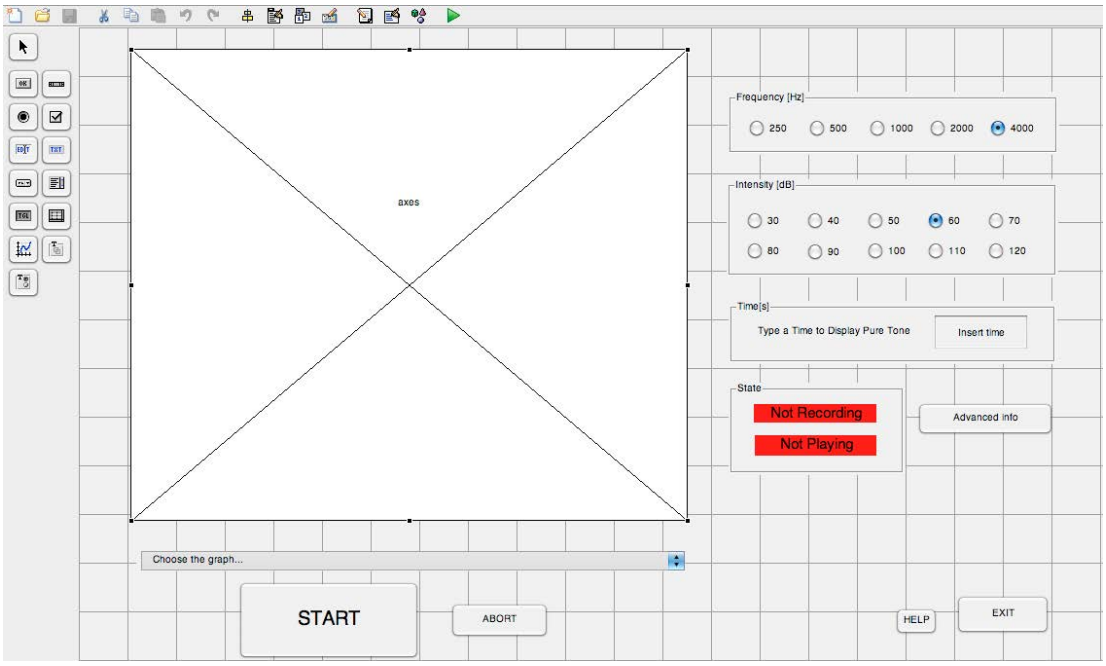

FIGURE 20: FINAL DESIGN PROOF OF CONCEPT GUI

Among all the possible elements, the MATLAB GUI designing tool includes: toggle button, sliding bar, radio button, check box button, text box, plot graph, editing text box, panel generator etc. Each one of the elements

has its own tag name identifier that will identify them in the script that is related to the GUI.

The final GUI contains the following elements:

- A frequency panel (tag: PanelFrequency) containing five different radio-buttons (only one can be selected at a time; tag: rBtFreq1…2,3,4,5) of five different frequency values in Hz. In figure 21 the radio=button of 250, 500, 1000, 2000 and 4000 Hz appear. This frequency will define the frequency of the sine wave.

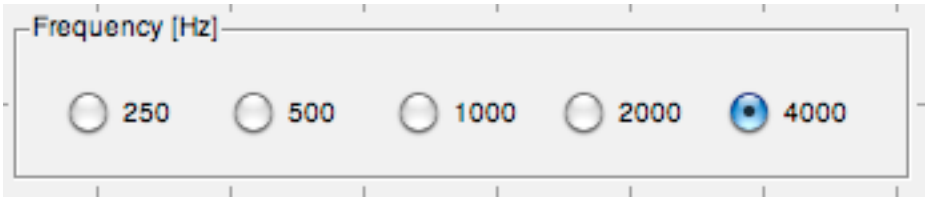

FIGURE 21: GUI FREQUENCY PANEL

- An intensity panel (tag: PanelIntensity) containing ten different radio buttons with dB values that will determine (depending on the coefficients of the script; tag: rBtIntensity1…2,3,4,5,6,7,8,9,10) the amplitude of the generated sine wave.

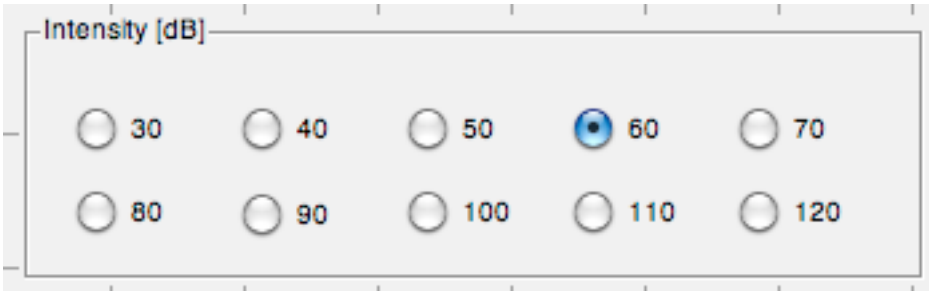

FIGURE 22: GUI INTENSITY PANEL

- A time panel (tag: PanelTime) containing a time editing box (where “Insert time” is written; tag: txtTime) in which the user has to write the time that the sine wave lasts.

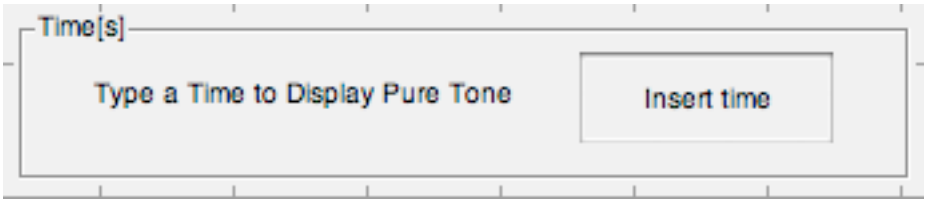

FIGURE 23: GUI TIME PANEL

- A state panel (tag: PanelState) with two texts: the one above (tag: txtRecording) is in red when the computer is not recording the sound that comes back from the circuit and is in green when it is recording. The one below (tag: txtPlaying) is in red when the pure tone is noting been played and green when the pure tone is been played.

FIGURE 24: GUI STATE PANEL

- The advanced info toggle button (tag: BtAdvancedInfo) shows some of the internal parameters that take part in the script such as the dB coefficients, the number of samples recorded etc.

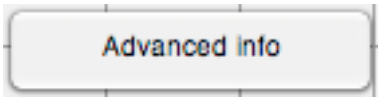

FIGURE 25: GUI ADVANCED INFO BUTTON

- The help toggle button (tag: BtHelp) pops up a text box that briefly explains how to use the script of MATLAB.

FIGURE 26: GUI HELP BUTTON

- The start button (tag: BtStart) triggers the generation of a pure tone of a time specified in the time panel, and with the selected

frequency and intensity of both the frequency and intensity panel. It also generates the trigger signal for the averaging process.

FIGURE 27: GUI START BUTTON

- The abort toggle button (tag:BtAbort) is for stopping the process whenever the user wants.

FIGURE 28: GUI ABORT BUTTON

- In the graph (tag: axes) windows several script outputs can be displayed.

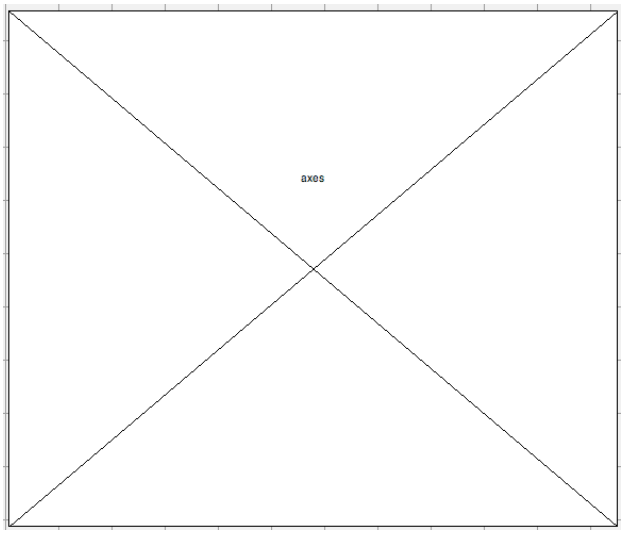

FIGURE 29: GUI AXIS SCREEN

- The pop up menu (tag: pum) displays several options. Each option output is shown in the graph component of figure 29.

FIGURE 30: GUI POP-UP MENU

Additionally a toolbar has been added to the interface, including a zoom-in, zoom-out, point cursor and a displacement tool (hand).

FIGURE 31: GUI TOOLBAR

Whenever the MATLAB script is run, the interface shown is the one in figure 31.

FIGURE 32: GUI INTERFACE

4.3.3 MATLAB CODE DESCRIPTION

In this section the MATLAB code script called test_PMC will be described. The MATLAB programming style used in this script is according with the guidelines from Columbia University (EEUU) (Johnson, 2002)

```
% --- Executes just before test_PMC is made visible.
function test_PMC_OpeningFcn(hObject, eventdata, handles, varargin)

handles.output = hObject;

global Params Coeff;
Params=ini2struct('CONFIG.ini');
Coeff=ini2struct('CALIB.ini');

% Update handles structure
guidata(hObject, handles);
```

CODE 1

In code 1, we take the information from two .ini files (the extension .ini is a type of configuration text file that is composed of parameters and values or properties) and we store them into two different structs (Params and coeff) with the MATLAB function ini2struct. Each value name inside the .ini file is the name of the value inside the struct. Both structs are turned global in order to be accessed from the whole script. This function runs only once before the GUI is shown. In the CONFIG.ini file we have store parameters such as the sampling rate (Fs), number of bits (nBits), default values to run the program in case the user has not yet selected any element of the GUI (AcqTime, AcqFreq, AcqIntensity), default values that appear on both the GUI frequency and GUI intensity panel. Other parameters are also initialized so as to use this values along the script. CALIB.ini file stores the values of the coefficients that define the amplitude of the pure tone for each dB value. In code 2, the predefined values of frequency and intensity from the .ini files are put into the GUI frequency and intensity panels.

```
% Set the values of PanelFrequency to the CONFIG parameters

% --- Executes during object creation, after setting all properties.
function rBtFreq1_CreateFcn(hObject, eventdata, handles)
global Params
aux=num2str(Params.Freq1);
set(hObject, 'String', Params.Freq1);

% --- Executes during object creation, after setting all properties.
function rBtFreq2_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Freq2);

% --- Executes during object creation, after setting all properties.
function rBtFreq3_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Freq3);

% --- Executes during object creation, after setting all properties.
function rBtFreq4_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Freq4);

% --- Executes during object creation, after setting all properties.
function rBtFreq5_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Freq5);

% Set the values of PanelIntensity to the CONFIG parameters

% --- Executes during object creation, after setting all properties.
function rBtIntensity1_CreateFcn(hObject, eventdata, handles)
global Params
```

```
set(hObject, 'String', Params.Intensity1);

% --- Executes during object creation, after setting all properties.
function rBtIntensity2_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity2);

% --- Executes during object creation, after setting all properties.
function rBtIntensity3_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity3);

% --- Executes during object creation, after setting all properties.
function rBtIntensity4_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity4);

% --- Executes during object creation, after setting all properties.
function rBtIntensity5_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity5);

% --- Executes during object creation, after setting all properties.
function rBtIntensity6_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity6);

% --- Executes during object creation, after setting all properties.
function rBtIntensity7_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity7);

% --- Executes during object creation, after setting all properties.
function rBtIntensity8_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity8);

% --- Executes during object creation, after setting all properties.
function rBtIntensity9_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity9);

% --- Executes during object creation, after setting all properties.
function rBtIntensity10_CreateFcn(hObject, eventdata, handles)
global Params
set(hObject, 'String', Params.Intensity10);
```

CODE 2

Figure code 3 shows the lines that run when the GUI start button has been pressed. First we call a function that will create the object where the recorded signal is going to be kept (code 4); this object (hRec) is created with the sampling frequency and nBits from the CONFIG.ini file; whenever the MATLAB record command starts recording, the code turns the GUI state

panel into green and changes its text to “recording”, if the record command stops recording, the code turns it into red and changes the text to “not recording. The record command records for a time defined inside the CONFIG.ini file (In the code, this time is in Params.TimeRec)

```
% --- Executes on button press in BtStart.
function BtStart_Callback(hObject, eventdata, handles)

global hPlay hRec Params;

create_recorder (handles);
create_player (handles);
record (hRec,Params.TimeRec);
disp('Recording...');
pause (Params.PauseTime);
disp ('Playing...');
play (hPlay);
```

CODE 3

```
function create_recorder (handles)
global hRec Params;
Fs=Params.Fs;
nBits=Params.nBits;
hRec= audiorecorder(Fs, nBits, 1);
hRec.StartFcn={@RecStarts_callback, handles};
hRec.StopFcn={@RecStops_callback, handles};

---

function RecStarts_callback (Obj, event, handles)
set(handles.txtRecording, 'BackgroundColor', [0 1 0]);
set(handles.txtRecording, 'String','Recording');

---

function RecStops_callback (Obj, event, handles)
set(handles.txtRecording, 'BackgroundColor',[1 0 0]);
set(handles.txtRecording, 'String','Not Recording');
```

CODE 4

Secondly in code 3, we call the function “create_player” that will create the object containing the signal that will be played (code 5). The function “create_sine” is called in order to generate a sine wave (pure tone). The sine formula is sine(2*pi*frequency*time)*amplitude. In this function the GUI radio-buttons determine the values used in the sine formula (frequency and amplitude). The sine wave is stored in the variable AudioData and is placed inside the object (hPlay) with the MATLAB audioplayer command. Whenever the MATLAB play command starts playing the sine wave, the code turns the

GUI state panel into green and changes its text to “playing”, if the record command stops playing, the code turns it into red and changes the text to “not playing”.

```
function create_player (handles)
global hPlay Params
   [Params.AudioData]=create_sine();

   hPlay = audioplayer(Params.AudioData, Params.Fs);
   hPlay.StartFcn={@PlayStarts_callback, handles};
   hPlay.StopFcn={@PlayStops_callback, handles};
```

```
function [AudioData, t]= create_sine()
    global Params Coeff
    if Params.AcqIntensity == Params.Intensity1
        ampl=Coeff.Db1;
    elseif Params.AcqIntensity == Params.Intensity2
        ampl=Coeff.Db2;
    elseif Params.AcqIntensity == Params.Intensity3
        ampl=Coeff.Db3;
    elseif Params.AcqIntensity == Params.Intensity4
        ampl=Coeff.Db4;
    elseif Params.AcqIntensity == Params.Intensity5
        ampl=Coeff.Db5;
    elseif Params.AcqIntensity == Params.Intensity6
        ampl=Coeff.Db6;
    elseif Params.AcqIntensity == Params.Intensity7
        ampl=Coeff.Db7;
    elseif Params.AcqIntensity == Params.Intensity8
        ampl=Coeff.Db8;
    elseif Params.AcqIntensity == Params.Intensity9
        ampl=Coeff.Db9;
    elseif Params.AcqIntensity == Params.Intensity10
        ampl=Coeff.Db10;
    end;

    for i = 1:length(Params.AcqFreq)
        dt = 1/(Params.Fs);

        t = 0:dt:(Params.AcqTime);
        AudioData=sin(2*pi*(Params.AcqFreq)*t)*ampl;
        Params.AudioData=AudioData;

    end;
    Params.Time=t;
```

```
function PlayStarts_callback (Obj, event, handles)
global hRec Params;

set(handles.txtPlaying, 'BackgroundColor',[0 1 0]);
set(handles.txtPlaying, 'String','Playing');
disp ('sample=');
Params.SampleStartPlay=hRec.CurrentSample;
disp ( hRec.CurrentSample);
```

```
function PlayStops_callback (Obj, event, handles)
global hRec;
```

```
set(handles.txtPlaying, 'BackgroundColor',[1 0 0]);
set(handles.txtPlaying, 'String', 'Not Playing');
Params.SampleEndPlay=hRec.CurrentSample;
disp ( hRec.CurrentSample)
```

CODE 5

Thirdly in code 3, we start recording the hObj object and immediately we start playing the signal. The signal finishes and then it stops recording.

```
function BtAbort_Callback(hObject, eventdata, handles)

global hRec hPlay;
stop (hRec);
stop (hPlay);
```

CODE 6

The GUI abort button can be pressed at any moment, and the recording and playing functions will stop (code 6).

```
function BtHelp_Callback(hObject, eventdata, handles)

msgbox('1, Select a frequency. 2, Select an intensity. 3, Write the
time you want to display the pure tone. 4, Click on the START button.
5, Select in the pop up menu the option you want to display in the
graph window. HINT: Click ABORT if you want to abort the script.
HINT: Check CONFIG.ini and CALIB.ini files');
```

CODE 7

If the GUI help button is pressed, a message with a hint about how to use the script pops-up (code 7).

```
function BtExit_Callback(hObject, eventdata, handles)

close
```

CODE 8

When the GUI exit button is pressed the interface window closes (code 8).

```
% --- Executes on selection change in pum.
function pum_Callback(hObject, eventdata, handles)

global Params hRec
pum_values=get(handles.pum, 'Value');
```

```
set(handles.txtPum, 'String', pum_values)
signal=getaudiodata(hRec);

[Params.AudioData, Params.Time]=create_sine();
switch pum_values
    case 1
        axes(handles.axes)
        i1=imread('CCE.png');
        imshow(i1);

    case 2
        axes(handles.axes)
        plot(Params.Time,Params.AudioData, 'r');

    case 3
        onesTrigg=zeros(length(Params.AudioData),1);
        Params.TriggerOutput=onesTrigg;
        return_trigger();

        axes(handles.axes)
        plot(Params.Time,Params.TriggerOutput, 'c')
    case 4
        onesTrigg=zeros(length(Params.AudioData),1);
        Params.TriggerOutput=onesTrigg;
        return_trigger();

        avgfilt=
accumarray(Params.IndicesTrigger,Params.AudioData,[],@mean);
        axes(handles.axes)
        plot(1:length(avgfilt),avgfilt, 'b')
    case 5
        axes(handles.axes);
        plot (signal);
    case 6
        axes(handles.axes);
        pwelch (signal,[],[],[],Params.Fs);
end
```

```
    function return_trigger()
        global Params
        Params.TriggerOutput(1)=1;

        for i=2:length(Params.AudioData)
            if (i+1) <= length(Params.AudioData)

                if (Params.AudioData(i) < 0) &&
(Params.AudioData(i+1) > 0)
                    Params.TriggerOutput(i+1)=1;
                end;
            end;
        end;
        counter=2;
        Params.IndicesTrigger=Params.TriggerOutput;
        for i=1:length(Params.AudioData)
            if Params.IndicesTrigger(i) == 0
                Params.IndicesTrigger(i)=counter;
                counter=counter+1;
            end;
            if Params.IndicesTrigger(i) == 1
                counter=2;
            end;
```

```
        end;
```

CODE 9

Code 9 contains the lines of the script belonging to the pop-up menu. Each one of the options inside the menu has assigned a number; this number is switched, and depending on the option a different output is obtained. If case 1, an image is shown. If case 2, the sine wave generated is plotted (contained in the variable AudioData). If case 3, the function return_trigger returns a trigger signal; It first generates a vector (TriggerOutput) with zeros of the size of the sine wave generated before. Afterwards, a 1 is placed in TriggerOutput whenever in the pure tone a negative position is followed by another one positive. Inside return_trigger function another vector called IndicesTrigger is generated. It is build by taking the Trigger Output and applying a “for” loop. When a 1 is found, it keeps adding one value to the value in the next position (i.e.,TriggerOutput = [1 0 0 0 1 0 0 0 0 1 0 0 0], then the IndicesTrigger = [1 2 3 4 1 2 3 4 1 2 3] until another 1 is found and starts again. If case 4, taking advantage of the Indices trigger vector we make use of the MATLAB function accumarray in order to average the same position in every period of the sine wave generated (in other words, all the positions with a 1 will be averaged, all the positions with 2s will be averaged and so on). The output of case 4 is a single period sine wave. In case 5 the signal recorded is plotted. In case 6 the pwelch spectrum is plotted.

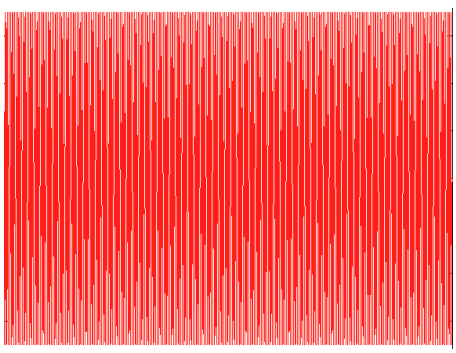

FIGURE 33: OUTPUT POP-UP MENU CASE 2

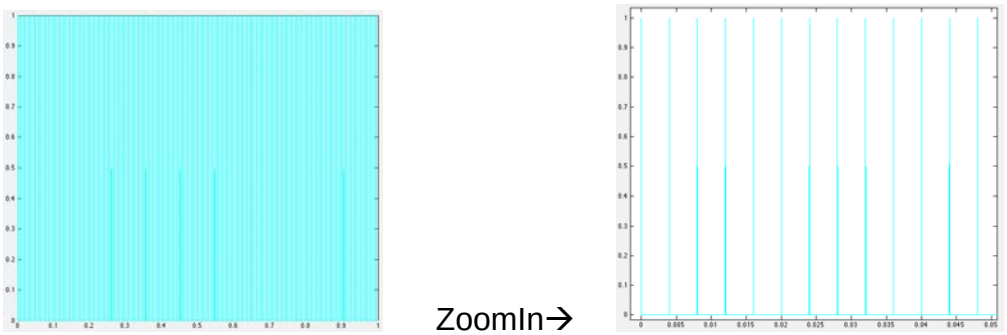

FIGURE 34: OUTPUT POP-UP MENU CASE 3 (TRIGGER SIGNAL)

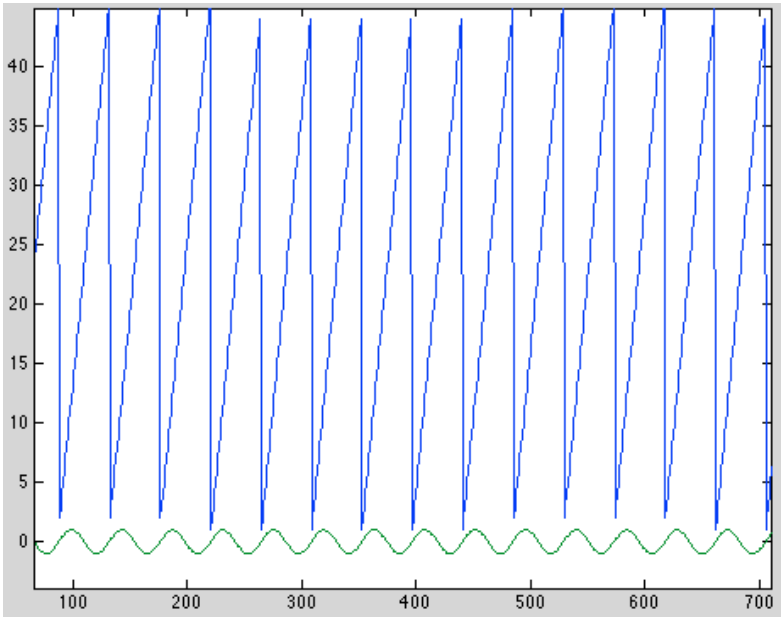

FIGURE 35: IN BLUE THE INDICESTRIGGER VECTOR. IN GREEN THE PURE TONE

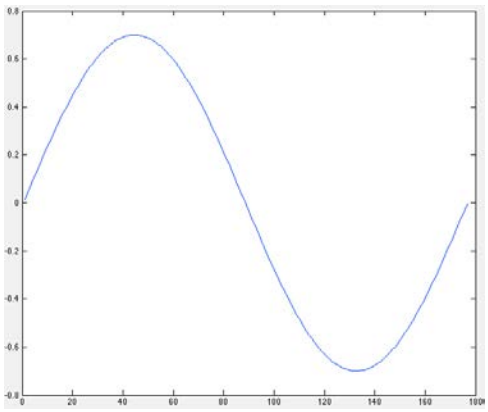

FIGURE 36: AVERAGED WAVE AFTER PERFORMING ACCUMARRAY FUNCTION ON THE PURE TONE

```
function txtTime_Callback(hObject, eventdata, handles)

global Params
Params.AcqTime=str2num(get(hObject, 'String'));

% --- Executes when selected object is changed in PanelFrequency.
function PanelFrequency_SelectionChangeFcn(hObject, eventdata,
handles)

global Params
Params.AcqFreq=str2num(get(hObject, 'String'));

% --- Executes when selected object is changed in PanelIntensity.
function PanelIntensity_SelectionChangeFcn(hObject, eventdata,
handles)
global Params
Params.AcqIntensity=str2num(get(hObject, 'String'));
```

CODE 10

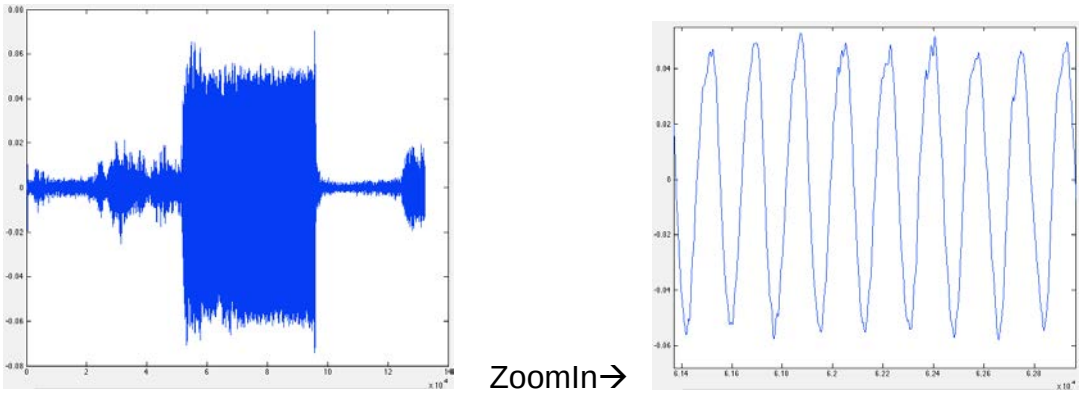

FIGURE 37: RECORDED SIGNAL OF CASE 5

4.3.4 DIGITAL FILTER

For our application, in order to reduce the amount of signal outside the frequency of interest, we have to design a peak filter, that is, a bandpass filter with narrow bandwidth, centered at the frequency of interest.

There are two types of digital filters: FIR and IIR. In table 8 some differences between FIR and IIR filters are shown.

FIR	IIR
The impulse response is non-zero for N samples only.	The impulse response duration is infinite.
Have no continuous time counterpart.	Are easily derived from continuous time filters.
They do not contain any poles in the z-domain.	Have both poles and zeros in the z-domain.
Linear phase can be easily achieved.	Linear phase cannot be easily approximated.

Always stable.	Unstable
Higher order than IIR filters is required.	Generally efficient

TABLE 8: FIR FILTERS VERSUS IIR FILTERS (ASSEM IBRAHIM, 2003)

MATLAB offers two filter tools to design your own digital filter: filterbuilder and fdatool. The main difference between them is that filterbuilder contains more feature responses than the fdatool, however this fact makes filterbuilder much more cumbersome.

In MATLAB there are different commands to apply the filter created with filterbuilder or fdatool to the signal. Considering that the filter delay is a significant concern as we intend to correlate the stimulus audio with the recorded signal, we opted for using the filtfilt function (for digital IIR filtering), which actually filters twice the signal (from left to right and vice versa), in such a way that the phase is zero. This can be done because the processing actually takes place offline.

Let's recall that the signal we record has an initial part where there is no signal, and another part where the pure tone response is recorded. Our procedure of filter analysis has two main steps: applying the filter to the signal without the pure tone and measure its power spectrum, and then applying the filter to the signal with the pure tone and measure its power spectrum again.

Code 11 is a different script from the script with GUI; the testing signal is a 1000 Hz pure tone with added white noise (in the code this signal is "acq") In code 11, we have implement an IIR peak filter (MATLAB command "iirpeak") whose inputs are the normalized frequency, the normalized bandwidth and the sampling frequency. The peak filter is centered at 1000 Hz and has 200 Hz of bandwidth is shown in figure 40.

```
Fs= 44100;   %sampling freq
Tt= 100;  % total time (msec)
Nsamples=Fs*Tt; %total samples
freq= 1000; %signal freq (Hz).
Nfreq= freq/Fs;  %normalized freq
L=round(Fs*Tt/1000); %Number samples to treat
t= 1:L; %time vector

l1=1000;    %segment to display
l2=1500;    %segment to display

mu=0;
sigma=10;
whiteNoise=sigma*randn(1,L)+mu;  % random white noise.
signal= sin(2*pi*freq/Fs*t); % create the pure tone signal
```

```
acq=signal+whiteNoise; % add signal and noise

pwelch (acq,[],[],[],Fs); % pwelch spectrum figure 38
figure(2), plot (t(l1:l2),signal(l1:l2), t(l1:l2), acq(l1:l2)); %
figure 39

% FILTER

freqNorm = freq/(Fs/2); % Normalized frequency
bandwidth = 200/(Fs/2); % Normalized bandwidth of 200 Hz.

[NUM,DEN]=iirpeak(freqNorm,bandwith, Fs);
fvtool(NUM,DEN); % Plot filter figure 40.

filteredSignal= filtfilt(NUM,DEN, acq);

figure (3), plot (t(l1:l2), filteredSignal(l1:l2)); % Plot filter
figure 41.

 figure(4);
 plot (t(l1:l2),signal(l1:l2), t(l1:l2),
figure(5)
pwelch (filteredSignal,[],[],[],Fs); % pwelch spectrum of the
filtered signal figure 42

% AVERAGING

ind=round(mod(1:L,Fs/freq)+1);
 % figure(6);
 % plot (1:L, ind, 1:L, signal);
avgfilt= accumarray(ind.',filteredSignal,[],@mean);
avgacq= accumarray(ind.',acq,[],@mean);
figure (7);

plot (1:size(avgfilt), avgfilt, 1:size(avgfilt), avgacq); % figure 43
```

CODE 11

In figure 38 we see the pwelch spectrum of signal “acq”. Note that the 1000 Hz frequency signal is barely visible among the white noise signal.

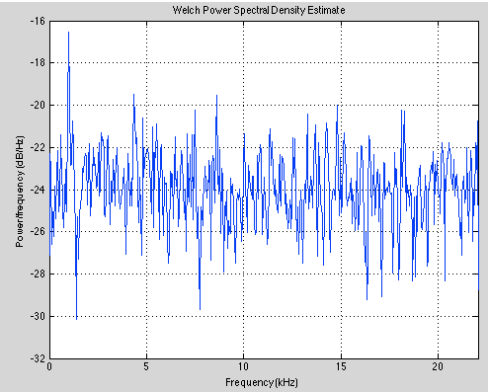

FIGURE 38

In figure 39, we plot the original sine wave generated (in blue) and “acq” (in green).

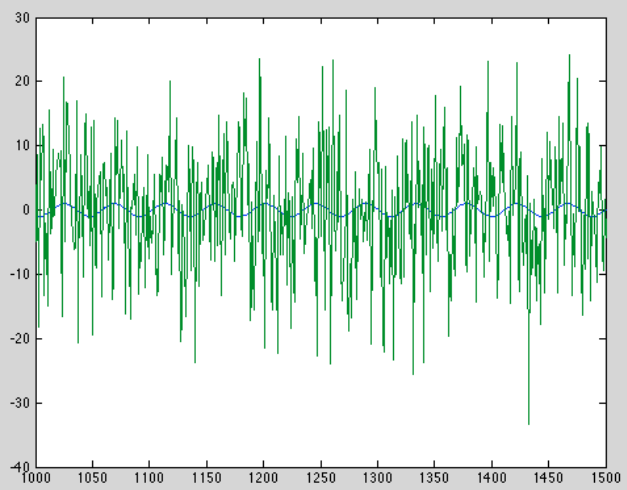

FIGURE 39

In figure 40, we show the peak filter designed to filter our acquired signal. It is centered in 1000 Hz and the bandwidth is of 200 Hz. If the bandwidth is too narrow it can lead to have the ripple effect on the plot of the digitally filtered signal; that is why we have increased the bandwidth up to 200 Hz.

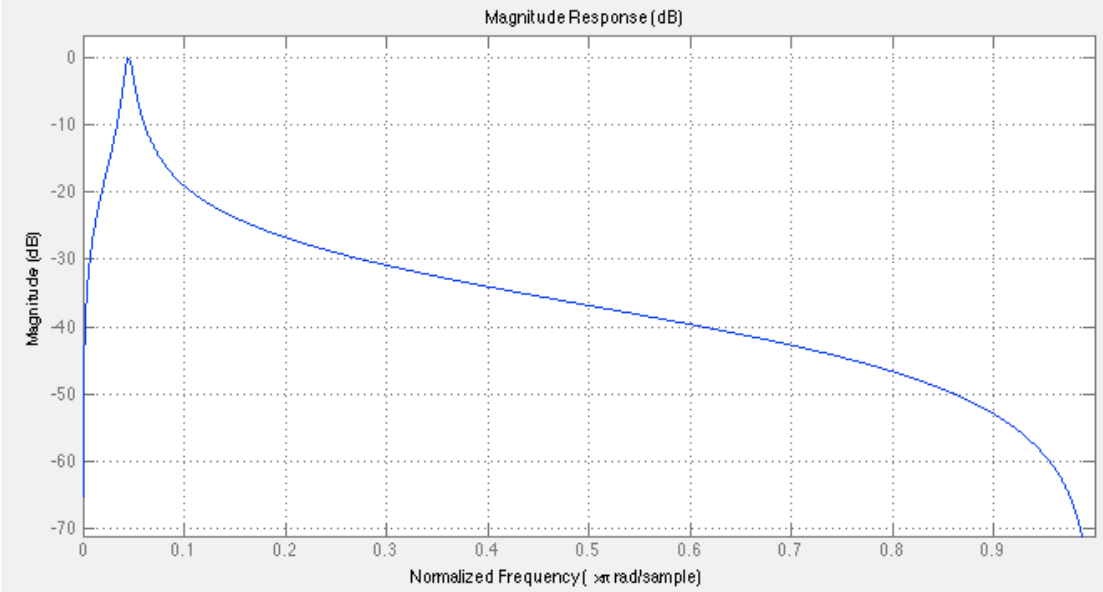

FIGURE 40

In figure 41, we plot the signal after passing the acq signal through the peak filter.

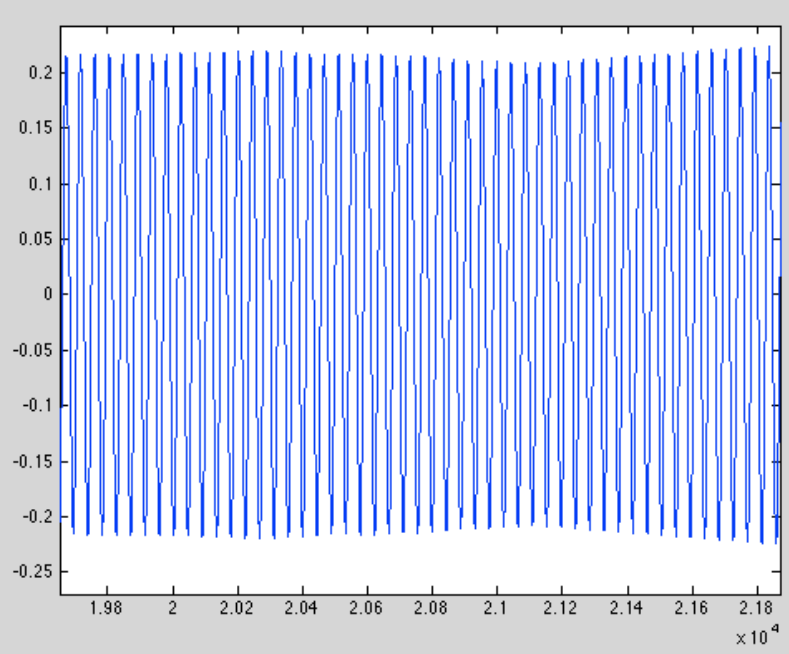

FIGURE 41

Figure 42, represents the pwelch spectrum of the filtered signal. It is observed that the 1000 Hz frequency component is perfectly defined.

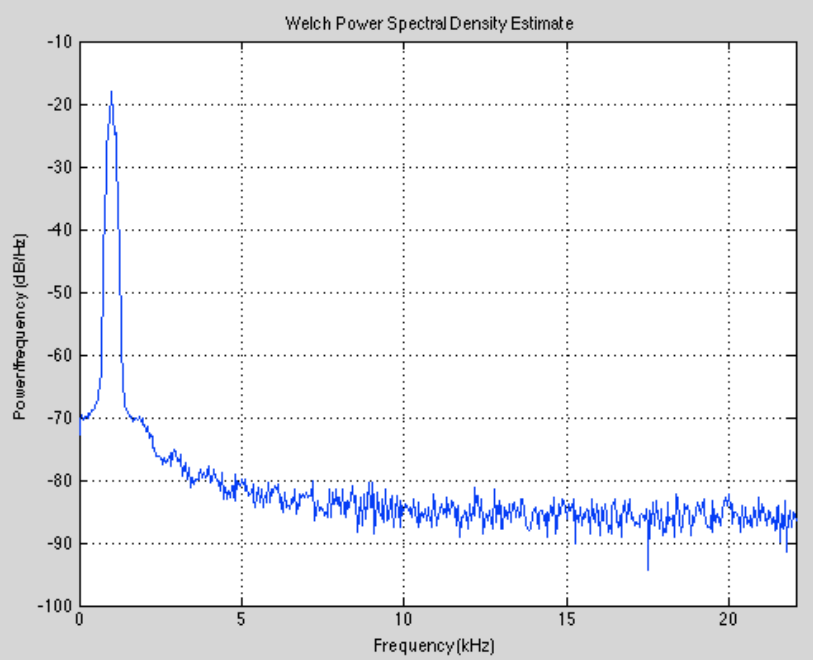

FIGURE 42

In figure 43, we plot the single-period wave generated by the MATLAB command accumarray of the signal (in green) recorded and the one (in blue) from the filtered signal.

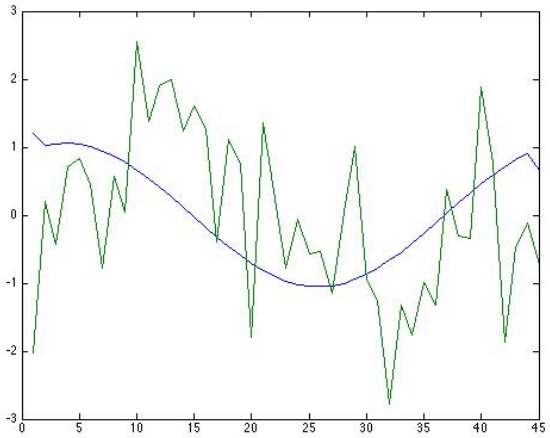

FIGURE 43

The peak digital filter seems to work properly and to be a good option in order to decrease the amount of hardware needed in the the CMP equipment.

“A conclusion is the place
where you get tired of thinking”

Arthur Bloch

5

CONCLUSIONS AND FUTURE WORK

5.1 Conclusions

The conclusions reached in this bachelor thesis are:

- The hearing system physiology, including an anatomical description of the structure (external ear, middle ear, and inner ear) has been reviewed. The cochlear microphonic potentials were also reviewed, focusing on its main characteristics and its possible use for audiometry. Besides, an equipment for detecting CMPs was described. The CMPs seems to be a reasonable option.

- A market pre-evaluation has been carried out. 5% of the worldwide population suffers from any kind of hearing loss, this is why research on this health problems should be increased. Thus increasing funding and legal protection policies in the hearing loss field. The funding source that has been selected is the European SME instrument as it fits our goals. Overall, the project seemed feasible.

- A proof of concept has been set up, based on new hardware equipment and a MATLAB software prototype- In preliminary tests the system worked correctly.

5.2 Future work

This bachelor thesis has been the first document related to the cochlear microphonic potentials in the IiSGM and it is intended to be a useful document for the future developments.

The things that are still missing are:

- Close the agreement with the “Zero Entropy” company.
- Apply to the European SME instrument for getting the ecomical resources needed.
- Taking on more staff to participate in the project.
- Write a complete business model.
- Develop and implement a definitive CMP equipment and software.
- Find the proper IPR protection strategy to protect the new technology.
- Get the CE marking.

“Believe you can and you’re
halfway there.”

Theodore Roosevelt

6

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